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PATENT APPLICATION
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First Inventor or Application Identifier Jiangchun Xu

Title

COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF PROSTATE CANCER

<b>D</b> ni	lly for nonprovisional applications under 37 CFR § 1.53(b)) Express Ma	ail Label No.	EL615230015US	
See M	APPLICATION ELEMENTS  1PEP chapter 600 concerning utility patent application contents.	ADDRESS	Box Patent Application Assistant Commissioner for Patents Washington, D.C. 20231	
1.	General Authorization Form & Fee Transmittal (Submit an original and a duplicate for fee processing)	Li	rofiche Computer Program (Appendix)	
2.	Specification [Total Pages] 201  (preferred arrangement set forth below)  - Descriptive Title of the Invention  - Cross References to Related Applications  - Statement Regarding Fed sponsored R & D  - Reference to Microfiche Appendix  - Background of the Invention	a. x C b. x P c. x S	ide and Amino Acid Sequence Submission able, all necessary) Computer-Readable Copy Paper Copy (identical to computer copy) Statement verifying identity of above copies	
	- Brief Summary of the Invention	ACCOM	PANYING APPLICATION PARTS	
	<ul> <li>Brief Description of the Drawings (if filed)</li> <li>Detailed Description</li> <li>Claim(s)</li> <li>Abstract of the Disclosure</li> </ul>	9. 37 CF (when	ignment Papers (cover sheet & document(s)) FR 3.73(b) Statement Power of Attorney n there is an assignee)	
3. [	x Drawing(s) (35 USC 113) [Total Sheets] 16	10. Eng	lish Translation Document (if applicable)	
4.	Oath or Declaration [Total Pages]		rmation Disclosure Copies of IDS ement (IDS)/PTO-1449 Citations	
5.	a. Newly executed (original or copy)  b. Copy from a prior application (37 CFR 1.63(d)) (for continuation/divisional with Box 17 completed)  i. DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b)  Incorporation By Reference (useable if box 4b is checked) The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered to be part of the disclosure of the accompanying application and is hereby incorporated by reference therein.	12. Prel 13. X Retu 14. Smal State 15. Cer (if for	liminary Amendment curn Receipt Postcard  all Entity Statement filed in prior application, status still proper and desired  retified Copy of Priority Document(s) reign priority is claimed) her: Certificate of Express Mail	
17.	If a CONTINUING APPLICATION, check appropriate box and  Continuation Divisional X Continuation-In		rior Application No.: <u>not assigned</u>	
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Respectfully submitted,

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## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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#### CERTIFICATE OF MAILING BY "EXPRESS MAIL"

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Respectfully submitted,

Seed Intellectual Property Law Group PLLC

Amber Straub/Jeanette West/Susan Johnson

**Enclosures:** 

Postcard
Form PTO/SB/05
Specification, Claims, Abstract (201 pages)
16 Sheets of Drawings (Figures 1-12)
Sequence Listing (357 pages)
Declaration for Sequence Listing
Diskette for Sequence Listing
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# COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF PROSTATE CANCER

## CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Patent Application No. 09/\_\_\_\_\_, filed May 12, 2000, which is a continuation-in-part of U.S. Patent Application 5 No. 09/568,100, filed May 9, 2000, which is a continuation-in-part of U.S. Patent Application No. 09/536,857, filed March 27, 2000, which is a continuation-in-part of U. S. Patent Application No. 09/483,672, filed January 14, 2000, which is a continuation-in-part of U.S. Patent Application No. 09/439,313, filed November 12, 1999, which is a continuation-in-part of U.S. Patent Application No. 09/352,616, filed July 13, 1999, which 10 is a continuation-in-part of U.S. Patent Application No. 09/288,946, filed April 9, 1999, which is a continuation-in-part of U.S. Patent Application No. 09/232,149, filed January 15, 1999, which is a continuation-in-part of U.S. Patent Application No. 09/159,812, filed September 23, 1998, which is a continuation-in-part of U.S. Patent Application No. 09/115,453, filed July 14, 1998, which is a continuation-in-part of U.S. Patent Application 15 No. 09/030,607, filed February 25, 1998, which is a continuation-in-part of U.S. Patent Application No. 09/020,956, filed February 9, 1998, which is a continuation-in-part of U.S. Patent Application No. 08/904,804, filed August 1, 1997, which is a continuation-in-part of U.S. Patent Application No. 08/806,099, filed February 25, 1997.

## 20 TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to therapy and diagnosis of cancer, such as prostate cancer. The invention is more specifically related to polypeptides comprising at least a portion of a prostate-specific protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides may be used in compositions for prevention and treatment of prostate cancer, and for the diagnosis and monitoring of such cancers.

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# BACKGROUND OF THE INVENTION

Cancer is a significant health problem throughout the world. Although Cancer is a significant health problem throughout the world. Although advances have been made in detection and therapy of cancer, no vaccine or other universally successful method for prevention or treatment is currently available. Current therapies, which are generally based on a combination of chemotherapy or surgery and radiation, continue to prove inadequate in many patients.

Prostate cancer is the most common form of cancer among males, with an estimated incidence of 30% in men over the age of 50. Overwhelming clinical evidence shows that human prostate cancer has the propensity to metastasize to bone, and the disease appears to progress inevitably from androgen dependent to androgen refractory status, leading to increased patient mortality. This prevalent disease is currently the second leading cause of cancer death among men in the U.S.

In spite of considerable research into therapies for the disease, prostate cancer remains difficult to treat. Commonly, treatment is based on surgery and/or radiation therapy, but these methods are ineffective in a significant percentage of cases. Two previously identified prostate specific proteins - prostate specific antigen (PSA) and prostatic acid phosphatase (PAP) - have limited therapeutic and diagnostic potential. For example, PSA levels do not always correlate well with the presence of prostate cancer, being positive in a percentage of non-prostate cancer cases, including benign prostatic hyperplasia (BPH). Furthermore, PSA measurements correlate with prostate volume, and do not indicate the level of metastasis.

In spite of considerable research into therapies for these and other cancers, prostate cancer remains difficult to diagnose and treat effectively. Accordingly, there is a need in the art for improved methods for detecting and treating such cancers. The present invention fulfills these needs and further provides other related advantages.

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## SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compositions and methods for the diagnosis and therapy of cancer, such as prostate cancer. In one aspect, the present invention provides polypeptides comprising at least a portion of a prostate-specific protein, or a variant thereof. Certain portions and other variants are immunogenic, such that the ability of the variant to react with antigen-specific antisera is not substantially diminished. Within certain embodiments, the polypeptide comprises a sequence that is encoded by a polynucleotide sequence selected from the group consisting of: (a) sequences recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789; (b) variants of a sequence recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789; and (c) complements of a sequence of (a) or (b). In specific embodiments, the polypeptides of the present invention comprise at least a portion of a tumor protein that includes an amino acid sequence selected from the group consisting of sequences recited in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 706-708, 775, 776, 778 and 780, and variants thereof.

The present invention further provides polynucleotides that encode a polypeptide as described above, or a portion thereof (such as a portion encoding at least 15 amino acid residues of a prostate-specific protein), expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, immunogenic compositions, or vaccines for prophylactic or therapeutic use are provided. Such

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compositions comprise a polypeptide or polynucleotide as described above and an immunostimulant.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a prostate-specific protein; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, immunogenic compositions, or vaccines, are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

Within related aspects, pharmaceutical compositions comprising a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a physiologically acceptable carrier are provided.

Compositions are further provided, within other aspects, that comprise a fusion protein, or a polynucleotide encoding a fusion protein, in combination with an immunostimulant.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a composition as recited above. The patient may be afflicted with prostate cancer, in which case the methods provide treatment for the disease, or patient considered at risk for such a disease may be treated prophylactically.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a prostate-specific protein, wherein the step of

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contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a prostate-specific protein, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polypucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of a prostate-specific protein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

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Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody. The cancer may be prostate cancer.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of:
(a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate-specific protein; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate-specific protein; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample

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obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

## BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE IDENTIFIERS

Figure 1 illustrates the ability of T cells to kill fibroblasts expressing the representative prostate-specific polypeptide P502S, as compared to control fibroblasts. The percentage lysis is shown as a series of effector:target ratios, as indicated.

Figures 2A and 2B illustrate the ability of T cells to recognize cells expressing the representative prostate-specific polypeptide P502S. In each case, the number of γ-interferon spots is shown for different numbers of responders. In Figure 2A, data is presented for fibroblasts pulsed with the P2S-12 peptide, as compared to fibroblasts pulsed with a control E75 peptide. In Figure 2B, data is presented for fibroblasts expressing P502S, as compared to fibroblasts expressing HER-2/neu.

Figure 3 represents a peptide competition binding assay showing that the P1S#10 peptide, derived from P501S, binds HLA-A2. Peptide P1S#10 inhibits HLA-A2 restricted presentation of fluM58 peptide to CTL clone D150M58 in TNF release bioassay. D150M58 CTL is specific for the HLA-A2 binding influenza matrix peptide fluM58.

Figure 4 illustrates the ability of T cell lines generated from P1S#10 immunized mice to specifically lyse P1S#10-pulsed Jurkat A2Kb targets and P501S-

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transduced Jurkat A2Kb targets, as compared to EGFP-transduced Jurkat A2Kb. The percent lysis is shown as a series of effector to target ratios, as indicated.

Figure 5 illustrates the ability of a T cell clone to recognize and specifically lyse Jurkat A2Kb cells expressing the representative prostate-specific polypeptide P501S, thereby demonstrating that the P1S#10 peptide may be a naturally processed epitope of the P501S polypeptide.

Figures 6A and 6B are graphs illustrating the specificity of a CD8<sup>+</sup> cell line (3A-1) for a representative prostate-specific antigen (P501S). Figure 6A shows the results of a <sup>51</sup>Cr release assay. The percent specific lysis is shown as a series of effector:target ratios, as indicated. Figure 6B shows the production of interferon-gamma by 3A-1 cells stimulated with autologous B-LCL transduced with P501S, at varying effector:target rations as indicated.

Figure 7 is a Western blot showing the expression of P501S in baculovirus. Figure 8 illustrates the results of epitope mapping studies on P501S.

Figure 9 is a schematic representation of the P501S protein showing the location of transmembrane domains and predicted intracellular and extracellular domains.

Figure 10 is a genomic map showing the location of the prostate genes P775P, P704P, B305D, P712P and P774P within the Cat Eye Syndrome region of chromosome 22q11.2

Figure 11 shows the results of an ELISA assay to determine the specificity of rabbit polyclonal antisera raised against P501S.

Figures 12A(1), 12A(2), 12A(3), and B are the full-length cDNA (SEQ ID NO:591) and predicted amino acid (SEQ ID NO:592) sequences, respectively, for the clone P788P.

SEQ ID NO: 1 is the determined cDNA sequence for F1-13

SEQ ID NO: 2 is the determined 3' cDNA sequence for F1-12

SEQ ID NO: 3 is the determined 5' cDNA sequence for F1-12

SEQ ID NO: 4 is the determined 3' cDNA sequence for F1-16

SEQ ID NO: 5 is the determined 3' cDNA sequence for H1-1

SEQ ID NO: 6 is the determined 3' cDNA sequence for H1-9
SEQ ID NO: 7 is the determined 3' cDNA sequence for H1-4
SEQ ID NO: 8 is the determined 3' cDNA sequence for J1-17
SEQ ID NO: 9 is the determined 5' cDNA sequence for J1-17
SEQ ID NO: 10 is the determined 3' cDNA sequence for L1-12
SEQ ID NO: 11 is the determined 5' cDNA sequence for L1-12
SEQ ID NO: 12 is the determined 3' cDNA sequence for N1-1862
SEQ ID NO: 13 is the determined 5' cDNA sequence for N1-1862
SEQ ID NO: 14 is the determined 3' cDNA sequence for J1-13
SEQ ID NO: 15 is the determined 5' cDNA sequence for J1-13
SEQ ID NO: 16 is the determined 3' cDNA sequence for J1-19
SEQ ID NO: 17 is the determined 5' cDNA sequence for J1-19
SEQ ID NO: 18 is the determined 3' cDNA sequence for J1-25
SEQ ID NO: 19 is the determined 5' cDNA sequence for J1-25
SEQ ID NO: 20 is the determined 5' cDNA sequence for J1-24
SEQ ID NO: 21 is the determined 3' cDNA sequence for J1-24
SEQ ID NO: 22 is the determined 5' cDNA sequence for K1-58
SEQ ID NO: 23 is the determined 3' cDNA sequence for K1-58
SEQ ID NO: 24 is the determined 5' cDNA sequence for K1-63
SEQ ID NO: 25 is the determined 3' cDNA sequence for K1-63
SEQ ID NO: 26 is the determined 5' cDNA sequence for L1-4
SEQ ID NO: 27 is the determined 3' cDNA sequence for L1-4
SEQ ID NO: 28 is the determined 5' cDNA sequence for L1-14
SEQ ID NO: 29 is the determined 3' cDNA sequence for L1-14
SEQ ID NO: 30 is the determined 3' cDNA sequence for J1-12
SEQ ID NO: 31 is the determined 3' cDNA sequence for J1-16
SEQ ID NO: 32 is the determined 3' cDNA sequence for J1-21
SEQ ID NO: 33 is the determined 3' cDNA sequence for K1-48
SEQ ID NO: 34 is the determined 3' cDNA sequence for K1-55

	SEQ ID NO: 35 is the determined 3' cDNA sequence for L1-2
	SEQ ID NO: 36 is the determined 3' cDNA sequence for L1-6
	SEQ ID NO: 37 is the determined 3' cDNA sequence for N1-1858
	SEQ ID NO: 38 is the determined 3' cDNA sequence for N1-1860
5	SEQ ID NO: 39 is the determined 3' cDNA sequence for N1-1861
	SEQ ID NO: 40 is the determined 3' cDNA sequence for N1-1864
	SEQ ID NO: 41 is the determined cDNA sequence for P5
	SEQ ID NO: 42 is the determined cDNA sequence for P8
	SEQ ID NO: 43 is the determined cDNA sequence for P9
10	SEQ ID NO: 44 is the determined cDNA sequence for P18
	SEQ ID NO: 45 is the determined cDNA sequence for P20
	SEQ ID NO: 46 is the determined cDNA sequence for P29
	SEQ ID NO: 47 is the determined cDNA sequence for P30
	SEQ ID NO: 48 is the determined cDNA sequence for P34
15	SEQ ID NO: 49 is the determined cDNA sequence for P36
	SEQ ID NO: 50 is the determined cDNA sequence for P38
	SEQ ID NO: 51 is the determined cDNA sequence for P39
	SEQ ID NO: 52 is the determined cDNA sequence for P42
	SEQ ID NO: 53 is the determined cDNA sequence for P47
20	SEQ ID NO: 54 is the determined cDNA sequence for P49
	SEQ ID NO: 55 is the determined cDNA sequence for P50
	SEQ ID NO: 56 is the determined cDNA sequence for P53
	SEQ ID NO: 57 is the determined cDNA sequence for P55
	SEQ ID NO: 58 is the determined cDNA sequence for P60
25	SEQ ID NO: 59 is the determined cDNA sequence for P64
	SEQ ID NO: 60 is the determined cDNA sequence for P65
	SEQ ID NO: 61 is the determined cDNA sequence for P73
	SEQ ID NO: 62 is the determined cDNA sequence for P75
	SEQ ID NO: 63 is the determined cDNA sequence for P76

		SEQ ID NO: 64 is the determined cDNA sequence for P79
		SEQ ID NO: 65 is the determined cDNA sequence for P84
		SEQ ID NO: 66 is the determined cDNA sequence for P68
		SEQ ID NO: 67 is the determined cDNA sequence for P80 (also referred to
:	5 as P704P)	
		SEQ ID NO: 68 is the determined cDNA sequence for P82
		SEQ ID NO: 69 is the determined cDNA sequence for U1-3064
		SEQ ID NO: 70 is the determined cDNA sequence for U1-3065
		SEQ ID NO: 71 is the determined cDNA sequence for V1-3692
1	0	SEQ ID NO: 72 is the determined cDNA sequence for 1A-3905
		SEQ ID NO: 73 is the determined cDNA sequence for V1-3686
		SEQ ID NO: 74 is the determined cDNA sequence for R1-2330
		SEQ ID NO: 75 is the determined cDNA sequence for 1B-3976
		SEQ ID NO: 76 is the determined cDNA sequence for V1-3679
1	5	SEQ ID NO: 77 is the determined cDNA sequence for 1G-4736
		SEQ ID NO: 78 is the determined cDNA sequence for 1G-4738
		SEQ ID NO: 79 is the determined cDNA sequence for 1G-4741
		SEQ ID NO: 80 is the determined cDNA sequence for 1G-4744
		SEQ ID NO: 81 is the determined cDNA sequence for 1G-4734
2	0	SEQ ID NO: 82 is the determined cDNA sequence for 1H-4774
		SEQ ID NO: 83 is the determined cDNA sequence for 1H-4781
		SEQ ID NO: 84 is the determined cDNA sequence for 1H-4785
		SEQ ID NO: 85 is the determined cDNA sequence for 1H-4787
		SEQ ID NO: 86 is the determined cDNA sequence for 1H-4796
2	5	SEQ ID NO: 87 is the determined cDNA sequence for 1I-4807
		SEQ ID NO: 88 is the determined cDNA sequence for 1I-4810
		SEQ ID NO: 89 is the determined cDNA sequence for 1I-4811
		SEQ ID NO: 90 is the determined cDNA sequence for 1J-4876
		SEQ ID NO: 91 is the determined cDNA sequence for 1K-4884

	SEQ ID NO: 92 is the determined cDNA sequence for 1K-4896
	SEQ ID NO: 93 is the determined cDNA sequence for 1G-4761
	SEQ ID NO: 94 is the determined cDNA sequence for 1G-4762
	SEQ ID NO: 95 is the determined cDNA sequence for 1H-4766
5	SEQ ID NO: 96 is the determined cDNA sequence for 1H-4770
	SEQ ID NO: 97 is the determined cDNA sequence for 1H-4771
	SEQ ID NO: 98 is the determined cDNA sequence for 1H-4772
	SEQ ID NO: 99 is the determined cDNA sequence for 1D-4297
	SEQ ID NO: 100 is the determined cDNA sequence for 1D-4309
10	SEQ ID NO: 101 is the determined cDNA sequence for 1D.1-4278
	SEQ ID NO: 102 is the determined cDNA sequence for 1D-4288
	SEQ ID NO: 103 is the determined cDNA sequence for 1D-4283
	SEQ ID NO: 104 is the determined cDNA sequence for 1D-4304
	SEQ ID NO: 105 is the determined cDNA sequence for 1D-4296
15	SEQ ID NO: 106 is the determined cDNA sequence for 1D-4280
	SEQ ID NO: 107 is the determined full length cDNA sequence for F1-12
	(also referred to as P504S)
	SEQ ID NO: 108 is the predicted amino acid sequence for F1-12
	SEQ ID NO: 109 is the determined full length cDNA sequence for J1-17
20	SEQ ID NO: 110 is the determined full length cDNA sequence for L1-12
	(also referred to as P501S)
	SEQ ID NO: 111 is the determined full length cDNA sequence for N1-1862
	(also referred to as P503S)
	SEQ ID NO: 112 is the predicted amino acid sequence for J1-17
25	SEQ ID NO: 113 is the predicted amino acid sequence for L1-12 (also
	referred to as P501S)
	SEQ ID NO: 114 is the predicted amino acid sequence for N1-1862 (also
	referred to as P503S)
	SEQ ID NO: 115 is the determined cDNA sequence for P89

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SEQ ID NO: 116 is the determined cDNA sequence for P90 SEQ ID NO: 117 is the determined cDNA sequence for P92 SEQ ID NO: 118 is the determined cDNA sequence for P95 SEQ ID NO: 119 is the determined cDNA sequence for P98 SEQ ID NO: 120 is the determined cDNA sequence for P102 SEO ID NO: 121 is the determined cDNA sequence for P110 SEQ ID NO: 122 is the determined cDNA sequence for P111 SEQ ID NO: 123 is the determined cDNA sequence for P114 SEQ ID NO: 124 is the determined cDNA sequence for P115 SEQ ID NO: 125 is the determined cDNA sequence for P116 SEQ ID NO: 126 is the determined cDNA sequence for P124 SEQ ID NO: 127 is the determined cDNA sequence for P126 SEQ ID NO: 128 is the determined cDNA sequence for P130 SEQ ID NO: 129 is the determined cDNA sequence for P133 SEQ ID NO: 130 is the determined cDNA sequence for P138 SEQ ID NO: 131 is the determined cDNA sequence for P143 SEQ ID NO: 132 is the determined cDNA sequence for P151 SEQ ID NO: 133 is the determined cDNA sequence for P156 SEQ ID NO: 134 is the determined cDNA sequence for P157 SEQ ID NO: 135 is the determined cDNA sequence for P166 SEQ ID NO: 136 is the determined cDNA sequence for P176 SEQ ID NO: 137 is the determined cDNA sequence for P178 SEQ ID NO: 138 is the determined cDNA sequence for P179 SEQ ID NO: 139 is the determined cDNA sequence for P185 SEQ ID NO: 140 is the determined cDNA sequence for P192 SEQ ID NO: 141 is the determined cDNA sequence for P201 SEQ ID NO: 142 is the determined cDNA sequence for P204 SEQ ID NO: 143 is the determined cDNA sequence for P208 SEQ ID NO: 144 is the determined cDNA sequence for P211

SEQ ID NO: 145 is the determined cDNA sequence for P213
SEQ ID NO: 146 is the determined cDNA sequence for P219
SEQ ID NO: 147 is the determined cDNA sequence for P237
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SEQ ID NO: 149 is the determined cDNA sequence for P248
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SEQ ID NO: 162 is the determined cDNA sequence for P107
SEQ ID NO: 163 is the determined cDNA sequence for P137
SEQ ID NO: 164 is the determined cDNA sequence for P194
SEQ ID NO: 165 is the determined cDNA sequence for P195
SEQ ID NO: 166 is the determined cDNA sequence for P196
SEQ ID NO: 167 is the determined cDNA sequence for P220
SEQ ID NO: 168 is the determined cDNA sequence for P234
SEQ ID NO: 169 is the determined cDNA sequence for P235
SEQ ID NO: 170 is the determined cDNA sequence for P243
SEQ ID NO: 171 is the determined cDNA sequence for P703P-DE1
SEQ ID NO: 172 is the predicted amino acid sequence for P703P-DE1
SEQ ID NO: 173 is the determined cDNA sequence for P703P-DE2

SEQ ID NO: 174 is the determined cDNA sequence for P703P-DE6
SEQ ID NO: 175 is the determined cDNA sequence for P703P-DE13
SEQ ID NO: 176 is the predicted amino acid sequence for P703P-DE13
SEQ ID NO: 177 is the determined cDNA sequence for P703P-DE14
SEQ ID NO: 178 is the predicted amino acid sequence for P703P-DE14
SEQ ID NO: 179 is the determined extended cDNA sequence for 1G-4736
SEQ ID NO: 180 is the determined extended cDNA sequence for 1G-4738
SEQ ID NO: 181 is the determined extended cDNA sequence for 1G-4741
SEQ ID NO: 182 is the determined extended cDNA sequence for 1G-4744
SEQ ID NO: 183 is the determined extended cDNA sequence for 1H-4774
SEQ ID NO: 184 is the determined extended cDNA sequence for 1H-4781
SEQ ID NO: 185 is the determined extended cDNA sequence for 1H-4785
SEQ ID NO: 186 is the determined extended cDNA sequence for 1H-4787
SEQ ID NO: 187 is the determined extended cDNA sequence for 1H-4796
SEQ ID NO: 188 is the determined extended cDNA sequence for 1I-4807
SEQ ID NO: 189 is the determined 3' cDNA sequence for 1I-4810
SEQ ID NO: 190 is the determined 3' cDNA sequence for 1I-4811
SEQ ID NO: 191 is the determined extended cDNA sequence for 1J-4876
SEQ ID NO: 192 is the determined extended cDNA sequence for 1K-4884
SEQ ID NO: 193 is the determined extended cDNA sequence for 1K-4896
SEQ ID NO: 194 is the determined extended cDNA sequence for 1G-4761
SEQ ID NO: 195 is the determined extended cDNA sequence for 1G-4762
SEQ ID NO: 196 is the determined extended cDNA sequence for 1H-4766
SEQ ID NO: 197 is the determined 3' cDNA sequence for 1H-4770
SEQ ID NO: 198 is the determined 3' cDNA sequence for 1H-4771
SEQ ID NO: 199 is the determined extended cDNA sequence for 1H-4772
SEQ ID NO: 200 is the determined extended cDNA sequence for 1D-4309
SEQ ID NO: 201 is the determined extended cDNA sequence for 1D.1-4278
SEO ID NO: 202 is the determined extended cDNA sequence for 1D-4288

SEQ ID NO: 203 is the determined extended cDNA sequence for 1D-4283
SEQ ID NO: 204 is the determined extended cDNA sequence for 1D-4304
SEQ ID NO: 205 is the determined extended cDNA sequence for 1D-4296
SEQ ID NO: 206 is the determined extended cDNA sequence for 1D-4280
SEQ ID NO: 207 is the determined cDNA sequence for 10-d8fwd
SEQ ID NO: 208 is the determined cDNA sequence for 10-H10con
SEQ ID NO: 209 is the determined cDNA sequence for 11-C8rev
SEQ ID NO: 210 is the determined cDNA sequence for 7.g6fwd
SEQ ID NO: 211 is the determined cDNA sequence for 7.g6rev
SEQ ID NO: 212 is the determined cDNA sequence for 8-b5fwd
SEQ ID NO: 213 is the determined cDNA sequence for 8-b5rev
SEQ ID NO: 214 is the determined cDNA sequence for 8-b6fwd
SEQ ID NO: 215 is the determined cDNA sequence for 8-b6 rev
SEQ ID NO: 216 is the determined cDNA sequence for 8-d4fwd
SEQ ID NO: 217 is the determined cDNA sequence for 8-d9rev
SEQ ID NO: 218 is the determined cDNA sequence for 8-g3fwd
SEQ ID NO: 219 is the determined cDNA sequence for 8-g3rev
SEQ ID NO: 220 is the determined cDNA sequence for 8-h11rev
SEQ ID NO: 221 is the determined cDNA sequence for g-f12fwd
SEQ ID NO: 222 is the determined cDNA sequence for g-f3rev
SEQ ID NO: 223 is the determined cDNA sequence for P509S
SEQ ID NO: 224 is the determined cDNA sequence for P510S
SEQ ID NO: 225 is the determined cDNA sequence for P703DE5
SEQ ID NO: 226 is the determined cDNA sequence for 9-A11
SEQ ID NO: 227 is the determined cDNA sequence for 8-C6
SEQ ID NO: 228 is the determined cDNA sequence for 8-H7
SEQ ID NO: 229 is the determined cDNA sequence for JPTPN13
SEQ ID NO: 230 is the determined cDNA sequence for JPTPN14
SEQ ID NO: 231 is the determined cDNA sequence for JPTPN23

SEQ ID NO: 232 is the determined cDNA sequence for JPTPN24
SEQ ID NO: 233 is the determined cDNA sequence for JPTPN25
SEQ ID NO: 234 is the determined cDNA sequence for JPTPN30
SEQ ID NO: 235 is the determined cDNA sequence for JPTPN34
SEQ ID NO: 236 is the determined cDNA sequence for PTPN35
SEQ ID NO: 237 is the determined cDNA sequence for JPTPN36
SEQ ID NO: 238 is the determined cDNA sequence for JPTPN38
SEQ ID NO: 239 is the determined cDNA sequence for JPTPN39
SEQ ID NO: 240 is the determined cDNA sequence for JPTPN40
SEQ ID NO: 241 is the determined cDNA sequence for JPTPN41
SEQ ID NO: 242 is the determined cDNA sequence for JPTPN42
SEQ ID NO: 243 is the determined cDNA sequence for JPTPN45
SEQ ID NO: 244 is the determined cDNA sequence for JPTPN46
SEQ ID NO: 245 is the determined cDNA sequence for JPTPN51
SEQ ID NO: 246 is the determined cDNA sequence for JPTPN56
SEQ ID NO: 247 is the determined cDNA sequence for PTPN64
SEQ ID NO: 248 is the determined cDNA sequence for JPTPN65
SEQ ID NO: 249 is the determined cDNA sequence for JPTPN67
SEQ ID NO: 250 is the determined cDNA sequence for JPTPN76
SEQ ID NO: 251 is the determined cDNA sequence for JPTPN84
SEQ ID NO: 252 is the determined cDNA sequence for JPTPN85
SEQ ID NO: 253 is the determined cDNA sequence for JPTPN86
SEQ ID NO: 254 is the determined cDNA sequence for JPTPN87
SEQ ID NO: 255 is the determined cDNA sequence for JPTPN88
SEQ ID NO: 256 is the determined cDNA sequence for JP1F1
SEQ ID NO: 257 is the determined cDNA sequence for JP1F2
SEQ ID NO: 258 is the determined cDNA sequence for JP1C2
SEQ ID NO: 259 is the determined cDNA sequence for JP1B1
SEQ ID NO: 260 is the determined cDNA sequence for JP1B2

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SEQ ID NO: 261 is the determined cDNA sequence for JP1D3 SEQ ID NO: 262 is the determined cDNA sequence for JP1A4 SEQ ID NO: 263 is the determined cDNA sequence for JP1F5 SEQ ID NO: 264 is the determined cDNA sequence for JP1E6 SEQ ID NO: 265 is the determined cDNA sequence for JP1D6 SEQ ID NO: 266 is the determined cDNA sequence for JP1B5 SEQ ID NO: 267 is the determined cDNA sequence for JP1A6 SEQ ID NO: 268 is the determined cDNA sequence for JP1E8 SEQ ID NO: 269 is the determined cDNA sequence for JP1D7 SEQ ID NO: 270 is the determined cDNA sequence for JP1D9 SEQ ID NO: 271 is the determined cDNA sequence for JP1C10 SEQ ID NO: 272 is the determined cDNA sequence for JP1A9 SEQ ID NO: 273 is the determined cDNA sequence for JP1F12 SEQ ID NO: 274 is the determined cDNA sequence for JP1E12 SEQ ID NO: 275 is the determined cDNA sequence for JP1D11 SEQ ID NO: 276 is the determined cDNA sequence for JP1C11 SEQ ID NO: 277 is the determined cDNA sequence for JP1C12 SEQ ID NO: 278 is the determined cDNA sequence for JP1B12 SEQ ID NO: 279 is the determined cDNA sequence for JP1A12 SEQ ID NO: 280 is the determined cDNA sequence for JP8G2 SEQ ID NO: 281 is the determined cDNA sequence for JP8H1 SEQ ID NO: 282 is the determined cDNA sequence for JP8H2 SEQ ID NO: 283 is the determined cDNA sequence for JP8A3 SEQ ID NO: 284 is the determined cDNA sequence for JP8A4 SEQ ID NO: 285 is the determined cDNA sequence for JP8C3 SEQ ID NO: 286 is the determined cDNA sequence for JP8G4 SEQ ID NO: 287 is the determined cDNA sequence for JP8B6 SEQ ID NO: 288 is the determined cDNA sequence for JP8D6 SEQ ID NO: 289 is the determined cDNA sequence for JP8F5

	SEQ ID NO: 290 is the determined cDNA sequence for JP8A8
	SEQ ID NO: 291 is the determined cDNA sequence for JP8C7
	SEQ ID NO: 292 is the determined cDNA sequence for JP8D7
	SEQ ID NO: 293 is the determined cDNA sequence for P8D8
5	SEQ ID NO: 294 is the determined cDNA sequence for JP8E7
	SEQ ID NO: 295 is the determined cDNA sequence for JP8F8
	SEQ ID NO: 296 is the determined cDNA sequence for JP8G8
	SEQ ID NO: 297 is the determined cDNA sequence for JP8B10
	SEQ ID NO: 298 is the determined cDNA sequence for JP8C10
10	SEQ ID NO: 299 is the determined cDNA sequence for JP8E9
	SEQ ID NO: 300 is the determined cDNA sequence for JP8E10
	SEQ ID NO: 301 is the determined cDNA sequence for JP8F9
	SEQ ID NO: 302 is the determined cDNA sequence for JP8H9
	SEQ ID NO: 303 is the determined cDNA sequence for JP8C12
15	SEQ ID NO: 304 is the determined cDNA sequence for JP8E11
	SEQ ID NO: 305 is the determined cDNA sequence for JP8E12
	SEQ ID NO: 306 is the amino acid sequence for the peptide PS2#12
	SEQ ID NO: 307 is the determined cDNA sequence for P711P
	SEQ ID NO: 308 is the determined cDNA sequence for P712P
20	SEQ ID NO: 309 is the determined cDNA sequence for CLONE23
	SEQ ID NO: 310 is the determined cDNA sequence for P774P
	SEQ ID NO: 311 is the determined cDNA sequence for P775P
	SEQ ID NO: 312 is the determined cDNA sequence for P715P
	SEQ ID NO: 313 is the determined cDNA sequence for P710P
25	SEQ ID NO: 314 is the determined cDNA sequence for P767P
	SEQ ID NO: 315 is the determined cDNA sequence for P768P
	SEQ ID NO: 316-325 are the determined cDNA sequences of previously
	isolated genes

SEQ ID NO: 326 is the determined cDNA sequence for P703PDE5

SEQ ID NO: 327 is the predicted amino acid sequence for P703PDE5 SEQ ID NO: 328 is the determined cDNA sequence for P703P6.26 SEQ ID NO: 329 is the predicted amino acid sequence for P703P6.26 SEQ ID NO: 330 is the determined cDNA sequence for P703PX-23 5 SEQ ID NO: 331 is the predicted amino acid sequence for P703PX-23 SEQ ID NO: 332 is the determined full length cDNA sequence for P509S SEQ ID NO: 333 is the determined extended cDNA sequence for P707P (also referred to as 11-C9) SEQ ID NO: 334 is the determined cDNA sequence for P714P 10 SEQ ID NO: 335 is the determined cDNA sequence for P705P (also referred to as 9-F3) SEQ ID NO: 336 is the predicted amino acid sequence for P705P SEQ ID NO: 337 is the amino acid sequence of the peptide P1S#10 SEQ ID NO: 338 is the amino acid sequence of the peptide p5 15 SEQ ID NO: 339 is the predicted amino acid sequence of P509S SEQ ID NO: 340 is the determined cDNA sequence for P778P SEQ ID NO: 341 is the determined cDNA sequence for P786P SEQ ID NO: 342 is the determined cDNA sequence for P789P SEQ ID NO: 343 is the determined cDNA sequence for a clone showing 20 homology to Homo sapiens MM46 mRNA SEQ ID NO: 344 is the determined cDNA sequence for a clone showing homology to Homo sapiens TNF-alpha stimulated ABC protein (ABC50) mRNA SEQ ID NO: 345 is the determined cDNA sequence for a clone showing

SEQ ID NO: 345 is the determined cDNA sequence for a clone showing homology to Homo sapiens mRNA for E-cadherin

SEQ ID NO: 346 is the determined cDNA sequence for a clone showing homology to Human nuclear-encoded mitochondrial serine hydroxymethyltransferase (SHMT)

SEQ ID NO: 347 is the determined cDNA sequence for a clone showing homology to Homo sapiens natural resistance-associated macrophage protein2 (NRAMP2)

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SEQ ID NO: 348 is the determined cDNA sequence for a clone showing homology to Homo sapiens phosphoglucomutase-related protein (PGMRP)

SEQ ID NO: 349 is the determined cDNA sequence for a clone showing homology to Human mRNA for proteosome subunit p40

5 SEQ ID NO: 350 is the determined cDNA sequence for P777P

SEQ ID NO: 351 is the determined cDNA sequence for P779P

SEQ ID NO: 352 is the determined cDNA sequence for P790P

SEQ ID NO: 353 is the determined cDNA sequence for P784P

SEQ ID NO: 354 is the determined cDNA sequence for P776P

SEQ ID NO: 355 is the determined cDNA sequence for P780P

SEQ ID NO: 356 is the determined cDNA sequence for P544S

SEQ ID NO: 357 is the determined cDNA sequence for P745S

SEQ ID NO: 358 is the determined cDNA sequence for P782P

SEQ ID NO: 359 is the determined cDNA sequence for P783P

SEQ ID NO: 360 is the determined cDNA sequence for unknown 17984

SEQ ID NO: 361 is the determined cDNA sequence for P787P

SEQ ID NO: 362 is the determined cDNA sequence for P788P

SEQ ID NO: 363 is the determined cDNA sequence for unknown 17994

SEQ ID NO: 364 is the determined cDNA sequence for P781P

SEQ ID NO: 365 is the determined cDNA sequence for P785P

SEQ ID NO: 366-375 are the determined cDNA sequences for splice variants of B305D.

SEQ ID NO: 376 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 366.

SEQ ID NO: 377 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 372.

SEQ ID NO: 378 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 373.

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SEQ ID NO: 379 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 374.

SEQ ID NO: 380 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 375.

5 SEQ ID NO: 381 is the determined cDNA sequence for B716P.

SEQ ID NO: 382 is the determined full-length cDNA sequence for P711P.

SEQ ID NO: 383 is the predicted amino acid sequence for P711P.

SEQ ID NO: 384 is the cDNA sequence for P1000C.

SEQ ID NO: 385 is the cDNA sequence for CGI-82.

SEQ ID NO:386 is the cDNA sequence for 23320.

SEQ ID NO:387 is the cDNA sequence for CGI-69.

SEQ ID NO:388 is the cDNA sequence for L-iditol-2-dehydrogenase.

SEQ ID NO:389 is the cDNA sequence for 23379.

SEQ ID NO:390 is the cDNA sequence for 23381.

SEQ ID NO:391 is the cDNA sequence for KIAA0122.

SEQ ID NO:392 is the cDNA sequence for 23399.

SEQ ID NO:393 is the cDNA sequence for a previously identified gene.

SEQ ID NO:394 is the cDNA sequence for HCLBP.

SEQ ID NO:395 is the cDNA sequence for transglutaminase.

SEQ ID NO:396 is the cDNA sequence for a previously identified gene.

SEQ ID NO:397 is the cDNA sequence for PAP.

SEQ ID NO:398 is the cDNA sequence for Ets transcription factor PDEF.

SEQ ID NO:399 is the cDNA sequence for hTGR.

SEQ ID NO:400 is the cDNA sequence for KIAA0295.

SEQ ID NO:401 is the cDNA sequence for 22545.

SEQ ID NO:402 is the cDNA sequence for 22547.

SEQ ID NO:403 is the cDNA sequence for 22548.

SEQ ID NO:404 is the cDNA sequence for 22550.

SEQ ID NO:405 is the cDNA sequence for 22551.

	SEQ ID NO:406 is the cDNA sequence for 22552.
	SEQ ID NO:407 is the cDNA sequence for 22553 (also known as P1020C).
	SEQ ID NO:408 is the cDNA sequence for 22558.
	SEQ ID NO:409 is the cDNA sequence for 22562.
5	SEQ ID NO:410 is the cDNA sequence for 22565.
	SEQ ID NO:411 is the cDNA sequence for 22567.
	SEQ ID NO:412 is the cDNA sequence for 22568.
	SEQ ID NO:413 is the cDNA sequence for 22570.
	SEQ ID NO:414 is the cDNA sequence for 22571.
10	SEQ ID NO:415 is the cDNA sequence for 22572.
	SEQ ID NO:416 is the cDNA sequence for 22573.
	SEQ ID NO:417 is the cDNA sequence for 22573.
	SEQ ID NO:418 is the cDNA sequence for 22575.
	SEQ ID NO:419 is the cDNA sequence for 22580.
15	SEQ ID NO:420 is the cDNA sequence for 22581.
	SEQ ID NO:421 is the cDNA sequence for 22582.
	SEQ ID NO:422 is the cDNA sequence for 22583.
	SEQ ID NO:423 is the cDNA sequence for 22584.
	SEQ ID NO:424 is the cDNA sequence for 22585.
20	SEQ ID NO:425 is the cDNA sequence for 22586.
	SEQ ID NO:426 is the cDNA sequence for 22587.
	SEQ ID NO:427 is the cDNA sequence for 22588.
	SEQ ID NO:428 is the cDNA sequence for 22589.
	SEQ ID NO:429 is the cDNA sequence for 22590.
25	SEQ ID NO:430 is the cDNA sequence for 22591.
	SEQ ID NO:431 is the cDNA sequence for 22592.
	SEQ ID NO:432 is the cDNA sequence for 22593.
	SEQ ID NO:433 is the cDNA sequence for 22594.
	SEQ ID NO:434 is the cDNA sequence for 22595.

	SEQ ID NO:435 is the cDNA sequence for 22596.
	SEQ ID NO:436 is the cDNA sequence for 22847.
	SEQ ID NO:437 is the cDNA sequence for 22848.
	SEQ ID NO:438 is the cDNA sequence for 22849.
5	SEQ ID NO:439 is the cDNA sequence for 22851.
	SEQ ID NO:440 is the cDNA sequence for 22852.
	SEQ ID NO:441 is the cDNA sequence for 22853.
	SEQ ID NO:442 is the cDNA sequence for 22854.
	SEQ ID NO:443 is the cDNA sequence for 22855.
10	SEQ ID NO:444 is the cDNA sequence for 22856.
	SEQ ID NO:445 is the cDNA sequence for 22857.
	SEQ ID NO:446 is the cDNA sequence for 23601.
	SEQ ID NO:447 is the cDNA sequence for 23602.
	SEQ ID NO:448 is the cDNA sequence for 23605.
15	SEQ ID NO:449 is the cDNA sequence for 23606.
	SEQ ID NO:450 is the cDNA sequence for 23612.
	SEQ ID NO:451 is the cDNA sequence for 23614.
	SEQ ID NO:452 is the cDNA sequence for 23618.
	SEQ ID NO:453 is the cDNA sequence for 23622.
20	SEQ ID NO:454 is the cDNA sequence for folate hydrolase.
	SEQ ID NO:455 is the cDNA sequence for LIM protein.
	SEQ ID NO:456 is the cDNA sequence for a known gene.
	SEQ ID NO:457 is the cDNA sequence for a known gene.
	SEQ ID NO:458 is the cDNA sequence for a previously identified gene.
25	SEQ ID NO:459 is the cDNA sequence for 23045.
	SEQ ID NO:460 is the cDNA sequence for 23032.
	SEQ ID NO:461 is the cDNA sequence for 23054.
	SEQ ID NO:462-467 are cDNA sequences for known genes.
	SEQ ID NO:468-471 are cDNA sequences for P710P.

SEQ ID NO:472 is a cDNA sequence for P1001C.

SEQ ID NO: 473 is the determined cDNA sequence for a first splice variant of P775P (referred to as 27505).

SEQ ID NO: 474 is the determined cDNA sequence for a second splice variant of P775P (referred to as 19947).

SEQ ID NO: 475 is the determined cDNA sequence for a third splice variant of P775P (referred to as 19941).

SEQ ID NO: 476 is the determined cDNA sequence for a fourth splice variant of P775P (referred to as 19937).

SEQ ID NO: 477 is a first predicted amino acid sequence encoded by the sequence of SEQ ID NO: 474.

SEQ ID NO: 478 is a second predicted amino acid sequence encoded by the sequence of SEQ ID NO: 474.

SEQ ID NO: 479 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 475.

SEQ ID NO: 480 is a first predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 481 is a second predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 482 is a third predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 483 is a fourth predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 484 is the first 30 amino acids of the *M. tuberculosis* antigen 25 Ra12.

SEQ ID NO: 485 is the PCR primer AW025.

SEQ ID NO: 486 is the PCR primer AW003.

SEQ ID NO: 487 is the PCR primer AW027.

SEQ ID NO: 488 is the PCR primer AW026.

SEQ ID NO: 489-501 are peptides employed in epitope mapping studies.

SEQ ID NO: 502 is the determined cDNA sequence of the complementarity determining region for the anti-P503S monoclonal antibody 20D4.

SEQ ID NO: 503 is the determined cDNA sequence of the complementarity determining region for the anti-P503S monoclonal antibody JA1.

SEQ ID NO: 504 & 505 are peptides employed in epitope mapping studies.

SEQ ID NO: 506 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 8H2.

SEQ ID NO: 507 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 7H8.

SEQ ID NO: 508 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 2D4.

SEQ ID NO: 509-522 are peptides employed in epitope mapping studies.

SEQ ID NO: 523 is a mature form of P703P used to raise antibodies against

15 P703P.

SEQ ID NO: 524 is the putative full-length cDNA sequence of P703P.

SEQ ID NO: 525 is the predicted amino acid sequence encoded by SEQ ID

NO: 524.

SEQ ID NO: 526 is the full-length cDNA sequence for P790P.

SEQ ID NO: 527 is the predicted amino acid sequence for P790P.

SEQ ID NO: 528 & 529 are PCR primers.

SEQ ID NO: 530 is the cDNA sequence of a splice variant of SEQ ID NO:

366.

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SEQ ID NO: 531 is the cDNA sequence of the open reading frame of SEQ

25 ID NO: 530.

SEQ ID NO: 532 is the predicted amino acid encoded by the sequence of SEQ ID NO: 531.

SEQ ID NO: 533 is the DNA sequence of a putative ORF of P775P.

SEQ ID NO: 534 is the predicted amino acid sequence encoded by SEQ ID

NO: 533.

SEQ ID NO: 535 is a first full-length cDNA sequence for P510S.

SEQ ID NO: 536 is a second full-length cDNA sequence for P510S.

SEQ ID NO: 537 is the predicted amino acid sequence encoded by SEQ ID

NO: 535.

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SEQ ID NO: 538 is the predicted amino acid sequence encoded by SEQ ID

NO: 536.

SEQ ID NO: 539 is the peptide P501S-370.

10 SEQ ID NO: 540 is the peptide P501S-376.

SEQ ID NO: 541-551 are epitopes of P501S.

SEQ ID NO: 552 is an extended cDNA sequence for P712P.

SEQ ID NO: 553-568 are the amino acid sequences encoded by predicted open reading frames within SEQ ID NO: 552.

SEQ ID NO: 569 is an extended cDNA sequence for P776P.

SEQ ID NO: 570 is the determined cDNA sequence for a splice variant of P776P referred to as contig 6.

SEQ ID NO: 571 is the determined cDNA sequence for a splice variant of P776P referred to as contig 7.

SEQ ID NO: 572 is the determined cDNA sequence for a splice variant of P776P referred to as contig 14.

SEQ ID NO: 573 is the amino acid sequence encoded by a first predicted ORF of SEQ ID NO: 570.

SEQ ID NO: 574 is the amino acid sequence encoded by a second predicted ORF of SEQ ID NO: 570.

SEQ ID NO: 575 is the amino acid sequence encoded by a predicted ORF of SEQ ID NO: 571.

SEQ ID NO: 576-586 are amino acid sequences encoded by predicted ORFs of SEQ ID NO: 569.

SEQ ID NO: 587 is a DNA consensus sequence of the sequences of P767P and P777P.

SEQ ID NO: 588-590 are amino acid sequences encoded by predicted ORFs of SEQ ID NO: 587.

SEQ ID NO: 591 is an extended cDNA sequence for P1020C.

SEQ ID NO: 592 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: P1020C.

SEQ ID NO: 593 is a splice variant of P775P referred to as 50748.

SEQ ID NO: 594 is a splice variant of P775P referred to as 50717.SEQ ID

NO: 595 is a splice variant of P775P referred to as 45985.

SEQ ID NO: 596 is a splice variant of P775P referred to as 38769.

SEQ ID NO: 597 is a splice variant of P775P referred to as 37922.

SEQ ID NO: 598 is a splice variant of P510S referred to as 49274.

SEQ ID NO: 599 is a splice variant of P510S referred to as 39487.

SEQ ID NO: 600 is a splice variant of P504S referred to as 5167.16.

SEQ ID NO: 601 is a splice variant of P504S referred to as 5167.1.

SEQ ID NO: 602 is a splice variant of P504S referred to as 5163.46.

SEQ ID NO: 603 is a splice variant of P504S referred to as 5163.42.

SEQ ID NO: 604 is a splice variant of P504S referred to as 5163.34.

SEQ ID NO: 605 is a splice variant of P504S referred to as 5163.17.

SEQ ID NO: 606 is a splice variant of P501S referred to as 10640.

SEQ ID NO: 607-615 are the sequences of PCR primers.

SEQ ID NO: 616 is the determined cDNA sequence of a fusion of P703P

and PSA.

SEQ ID NO: 617 is the amino acid sequence of the fusion of P703P and

PSA.

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SEQ ID NO: 618-689 are determined cDNA sequences of prostate-specific

clones.

SEQ ID NO: 690 is the cDNA sequence of the gene DD3.

SEQ ID NO: 691-697 are determined cDNA sequences of prostate-specific clones.

SEQ ID NO: 698 is an extended cDNA sequence for P714P.

SEQ ID NO: 699-701 are the cDNA sequences for splice variants of P704P.

SEQ ID NO: 702 is the cDNA sequence of a spliced variant of P553S referred to as P553S-14.

SEQ ID NO: 703 is the cDNA sequence of a spliced variant of P553S referred to as P553S-12.

SEQ ID NO: 704 is the cDNA sequence of a spliced variant of P553S referred to as P553S-10.

SEQ ID NO: 705 is the cDNA sequence of a spliced variant of P553S referred to as P553S-6.

SEQ ID NO: 706 is the amino acid sequence encoded by SEQ ID NO: 705.

SEQ ID NO: 707 is the amino acid sequence encoded by SEQ ID NO: 702

SEQ ID NO: 708 is a second amino acid sequence encoded by SEO ID NO: 702.

SEQ ID NO: 709-772 are determined cDNA sequences of prostate-specific clones.

SEQ ID NO: 773 is a first full-length cDNA sequence for prostate-specific transglutaminase gene (also referred to herein as P558S).

SEQ ID NO: 774 is a second full-length cDNA sequence for prostate-specific transglutaminase gene.

SEQ ID NO: 775 is the amino acid sequence encoded by the sequence of SEQ ID NO: 773.

SEQ ID NO: 776 is the amino acid sequence encoded by the sequence of SEQ ID NO: 774.

SEQ ID NO: 777 is the full-length cDNA sequence for P788P.

SEQ ID NO: 778 is the amino acid sequence encoded by SEQ ID NO: 777.

SEQ ID NO: 779 is the determined cDNA sequence for a polymorphic variant of P788P.

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SEQ ID NO: 780 is the amino acid sequence encoded by SEQ ID NO: 779.

SEQ ID NO: 781 is the amino acid sequence of peptide 4 from P703P.

SEQ ID NO: 782 is the cDNA sequence that encodes peptide 4 from P703P.

SEQ ID NO: 783-798 are the cDNA sequence encoding epitopes of P703P.

SEQ ID NO: 799-814 are the amino acid sequences of epitopes of P703P.

## DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for using the compositions, for example in the therapy and diagnosis of cancer, such as prostate cancer. Certain illustrative compositions described herein include prostate-specific polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (e.g., T cells). A "prostate-specific protein," as the term is used herein, refers generally to a protein that is expressed in prostate cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in other normal tissues, as determined using a representative assay provided herein. Certain prostate-specific proteins are tumor proteins that react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera of a patient afflicted with prostate cancer.

Therefore, in accordance with the above, and as described further below, the present invention provides illustrative polynucleotide compositions having sequences set forth in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789, illustrative polypeptide compositions having amino acid sequences set forth in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 706-708, 775, 776, 778 and 780, antibody compositions capable of binding such polypeptides, and numerous additional embodiments employing such compositions, for example in the detection, diagnosis and/or therapy of human prostate cancer.

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#### POLYNUCLEOTIDE COMPOSITIONS

As used herein, the terms "DNA segment" and "polynucleotide" refer to a DNA molecule that has been isolated free of total genomic DNA of a particular species. Therefore, a DNA segment encoding a polypeptide refers to a DNA segment that contains one or more coding sequences yet is substantially isolated away from, or purified free from, total genomic DNA of the species from which the DNA segment is obtained. Included within the terms "DNA segment" and "polynucleotide" are DNA segments and smaller fragments of such segments, and also recombinant vectors, including, for example, plasmids, cosmids, phagemids, phage, viruses, and the like.

As will be understood by those skilled in the art, the DNA segments of this invention can include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally isolated, or modified synthetically by the hand of man.

"Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA segment does not contain large portions of unrelated coding DNA, such as large chromosomal fragments or other functional genes or polypeptide coding regions. Of course, this refers to the DNA segment as originally isolated, and does not exclude genes or coding regions later added to the segment by the hand of man.

As will be recognized by the skilled artisan, polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (i.e., an endogenous sequence that encodes a prostate-specific protein or a portion thereof) or may comprise a

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variant, or a biological or antigenic functional equivalent of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions, as further described below, preferably such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. The term "variants" also encompasses homologous genes of xenogenic origin.

When comparing polynucleotide or polypeptide sequences, two sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 Methods in Enzymology vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) CABIOS 5:151-153; Myers, E.W. and Muller W. (1988) CABIOS 4:11-17; Robinson, E.D. (1971) Comb. Theor 11:105; Santou, N. Nes, M. (1987) Mol. Biol. Evol. 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) Proc. Natl. Acad., Sci. USA 80:726-730.

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Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) Nucl. Acids Res. 25:3389-3402 and Altschul et al. (1990) J. Mol. Biol. 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). For amino acid sequences, a scoring matrix can be used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) Proc. Natl. Acad. Sci. USA 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and a comparison of both strands.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20

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positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Therefore, the present invention encompasses polynucleotide and polypeptide sequences having substantial identity to the sequences disclosed herein, for example those comprising at least 50% sequence identity, preferably at least 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence identity compared to a polynucleotide or polypeptide sequence of this invention using the methods described herein, (e.g., BLAST analysis using standard parameters, as described below). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like.

In additional embodiments, the present invention provides isolated polynucleotides and polypeptides comprising various lengths of contiguous stretches of sequence identical to or complementary to one or more of the sequences disclosed herein. For example, polynucleotides are provided by this invention that comprise at least about 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more contiguous nucleotides of one or more of the sequences disclosed herein as well as all intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted values, such as 16, 17, 18, 19, etc.; 21, 22, 23, etc.; 30, 31, 32, etc.; 50, 51, 52, 53, etc.; 100, 101, 102, 103, etc.; 150, 151, 152, 153, etc.; including all integers through 200-500; 500-1,000, and the like.

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The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative DNA segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 50 base pairs in length, and the like, (including all intermediate lengths) are contemplated to be useful in many implementations of this invention.

In other embodiments, the present invention is directed to polynucleotides that are capable of hybridizing under moderately stringent conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof. Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

Moreover, it will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an

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altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

## **PROBES AND PRIMERS**

In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a sequence region of at least about 15 nucleotide long contiguous sequence that has the same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, *e.g.*, those of about 20, 30, 40, 50, 100, 200, 500, 1000 (including all intermediate lengths) and even up to full length sequences will also be of use in certain embodiments.

The ability of such nucleic acid probes to specifically hybridize to a sequence of interest will enable them to be of use in detecting the presence of complementary sequences in a given sample. However, other uses are also envisioned, such as the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

Polynucleotide molecules having sequence regions consisting of contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in, *e.g.*, Southern and Northern blotting. This would allow a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also in various bacterial cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately depend on the intended use or application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the contiguous complementary region may be varied, such as between about 15 and about 100

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nucleotides, but larger contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having contiguous complementary sequences over stretches greater than 15 bases in length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having gene-complementary stretches of 15 to 25 contiguous nucleotides, or even longer where desired.

Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequence set forth in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789, or to any continuous portion of the sequence, from about 15-25 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various factors. For example, one may wish to employ primers from towards the termini of the total sequence.

Small polynucleotide segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCR<sup>TM</sup> technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other recombinant DNA techniques generally known to those of skill in the art of molecular biology.

The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene fragments of interest. Depending on the application envisioned, one will typically desire to employ varying conditions of hybridization to achieve varying degrees of selectivity of

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probe towards target sequence. For applications requiring high selectivity, one will typically desire to employ relatively stringent conditions to form the hybrids, *e.g.*, one will select relatively low salt and/or high temperature conditions, such as provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about 50°C to about 70°C. Such selective conditions tolerate little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for isolating related sequences.

Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less stringent (reduced stringency) hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any case, it is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide, which serves to destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

### 20 POLYNUCLEOTIDE IDENTIFICATION AND CHARACTERIZATION

Polynucleotides may be identified, prepared and/or manipulated using any of a variety of well established techniques. For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least two fold greater in a tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed, for example, using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena *et al.*, *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller *et al.*, *Proc. Natl. Acad. Sci. USA* 

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94:2150-2155, 1997). Alternatively, polynucleotides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as prostate-specific cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (e.g., a prostate tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with <sup>32</sup>P) using well known techniques. A bacterial or bacteriophage library is then generally screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences can then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available

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kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (see Triglia et al., Nucl. Acids Res. 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., PCR Methods Applic. 1:111-19, 1991) and walking PCR (Parker et al., Nucl. Acids. Res. 19:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence. Full length DNA sequences may also be obtained by analysis of genomic fragments.

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#### POLYNUCLEOTIDE EXPRESSION IN HOST CELLS

In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or functional equivalents thereof, may be used in recombinant DNA molecules to direct expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

As will be understood by those of skill in the art, it may be advantageous in some instances to produce polypeptide-encoding nucleotide sequences possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring sequence.

Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For example, DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. In addition, site-directed mutagenesis may be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be engineered to contain a cleavage site

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located between the polypeptide-encoding sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. *et al.* (1980) *Nucl. Acids Res. Symp. Ser.* 215-223, Horn, T. *et al.* (1980) *Nucl. Acids Res. Symp. Ser.* 225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. *et al.* (1995) *Science 269*:202-204) and automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (e.g., Creighton, T. (1983) Proteins, Structures and Molecular Principles, WH Freeman and Co., New York, N.Y.) or other comparable techniques available in the art. The composition of the synthetic peptides may be confirmed by amino acid analysis or sequencing (e.g., the Edman degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

In order to express a desired polypeptide, the nucleotide sequences encoding the polypeptide, or functional equivalents, may be inserted into appropriate expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding a polypeptide of interest and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. Such techniques are described in Sambrook, J. *et al.* (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. *et al.* (1989) Current Protocols in Molecular Biology, John Wiley & Sons, New York. N.Y.

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A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (e.g., baculovirus); plant cell systems transformed with virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems.

The "control elements" or "regulatory sequences" present in an expression vector are those non-translated regions of the vector--enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out transcription and translation. Such elements may vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, may be used. For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the PBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or PSPORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are generally preferred. If it is necessary to generate a cell line that contains multiple copies of the sequence encoding a polypeptide, vectors based on SV40 or EBV may be advantageously used with an appropriate selectable marker.

In bacterial systems, a number of expression vectors may be selected depending upon the use intended for the expressed polypeptide. For example, when large quantities are needed, for example for the induction of antibodies, vectors which direct high level expression of fusion proteins that are readily purified may be used. Such vectors include, but are not limited to, the multifunctional *E. coli* cloning and expression vectors such as BLUESCRIPT (Stratagene), in which the sequence encoding the polypeptide of interest may be ligated into the vector in frame with sequences for the amino-terminal Met and the subsequent 7 residues of .beta.-galactosidase so that a hybrid protein is produced;

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pIN vectors (Van Heeke, G. and S. M. Schuster (1989) *J. Biol. Chem. 264*:5503-5509); and the like pGEX Vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins made in such systems may be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

In the yeast, Saccharomyces cerevisiae, a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may be used. For reviews, see Ausubel *et al.* (supra) and Grant *et al.* (1987) *Methods Enzymol.* 153:516-544.

In cases where plant expression vectors are used, the expression of sequences encoding polypeptides may be driven by any of a number of promoters. For example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J. 6*:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. *et al.* (1984) *EMBO J. 3*:1671-1680; Broglie, R. *et al.* (1984) *Science 224*:838-843; and Winter, J. *et al.* (1991) *Results Probl. Cell Differ. 17*:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York, N.Y.; pp. 191-196).

An insect system may also be used to express a polypeptide of interest. For example, in one such system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in Spodoptera frugiperda cells or in Trichoplusia larvae. The sequences encoding the polypeptide may be cloned into a non-essential region of the virus, such as the polyhedrin gene, and placed under control of the

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polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses may then be used to infect, for example, S. frugiperda cells or Trichoplusia larvae in which the polypeptide of interest may be expressed (Engelhard, E. K. et al. (1994) *Proc. Natl. Acad. Sci. 91*:3224-3227).

In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci. 81*:3655-3659). In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. et al. (1994) Results Probl. Cell Differ. 20:125-162).

In addition, a host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired

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fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation. glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to facilitate correct insertion, folding and/or function. Different host cells such as CHO, HeLa, MDCK, HEK293, and WI38, which have specific cellular machinery and characteristic mechanisms for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a polynucleotide of interest may be transformed using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler, M. et al. (1977) Cell 11:223-32) and adenine phosphoribosyltransferase (Lowy, I. et al. (1990) Cell 22:817-23) genes which can be employed in tk.sup.- or aprt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. 77:3567-70); npt, which confers resistance to the aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. et al (1981) J. Mol. Biol. 150:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, supra). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman, S. C. and R. C.

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Mulligan (1988) *Proc. Natl. Acad. Sci.* 85:8047-51). Recently, the use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C. A. *et al.* (1995) *Methods Mol. Biol.* 55:121-131).

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a marker gene sequence, recombinant cells containing sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

Alternatively, host cells which contain and express a desired polynucleotide sequence may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies specific for the product are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. *et al.* (1990; Serological Methods, a Laboratory Manual, APS Press, St Paul. Minn.) and Maddox, D. E. *et al.* (1983; *J. Exp. Med. 158*:1211-1216).

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A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification using a labeled nucleotide. Alternatively, the sequences, or any portions thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits. Suitable reporter molecules or labels, which may be used include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with a polynucleotide sequence of interest may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a recombinant cell may be secreted or contained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides of the invention may be designed to contain signal sequences which direct secretion of the encoded polypeptide through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker sequences such as those specific for Factor XA or enterokinase (Invitrogen. San Diego, Calif.) between the purification domain and the encoded polypeptide may be used to facilitate purification. One such expression vector provides for expression of a fusion protein containing a polypeptide of interest and a

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nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification on IMIAC (immobilized metal ion affinity chromatography) as described in Porath, J. et al. (1992, Prot. Exp. Purif. 3:263-281) while the enterokinase cleavage site provides a means for purifying the desired polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. et al. (1993; DNA Cell Biol. 12:441-453).

In addition to recombinant production methods, polypeptides of the invention, and fragments thereof, may be produced by direct peptide synthesis using solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc.* 85:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.

#### SITE-SPECIFIC MUTAGENESIS

Site-specific mutagenesis is a technique useful in the preparation of individual peptides, or biologically functional equivalent polypeptides, through specific mutagenesis of the underlying polynucleotides that encode them. The technique, well-known to those of skill in the art, further provides a ready ability to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence changes into the DNA. Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

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In certain embodiments of the present invention, the inventors contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or more properties of the encoded polypeptide, such as the antigenicity of a polypeptide vaccine. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA molecule. In such embodiments, a primer comprising typically about 14 to about 25 nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phage are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

In general, site-directed mutagenesis in accordance herewith is performed by first obtaining a single-stranded vector or melting apart of two strands of a double-stranded vector that includes within its sequence a DNA sequence that encodes the desired peptide. An oligonucleotide primer bearing the desired mutated sequence is prepared, generally synthetically. This primer is then annealed with the single-stranded vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected which include recombinant vectors bearing the mutated sequence arrangement.

The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful

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species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.

As used herein, the term "oligonucleotide directed mutagenesis procedure" refers to template-dependent processes and vector-mediated propagation which result in an increase in the concentration of a specific nucleic acid molecule relative to its initial concentration, or in an increase in the concentration of a detectable signal, such as amplification. As used herein, the term "oligonucleotide directed mutagenesis procedure" is intended to refer to a process that involves the template-dependent extension of a primer molecule. The term template dependent process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known rules of complementary base pairing (see, for example, Watson, 1987). Typically, vector mediated methodologies involve the introduction of the nucleic acid fragment into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of the amplified nucleic acid fragment. Examples of such methodologies are provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in its entirety.

# POLYNUCLEOTIDE AMPLIFICATION TECHNIQUES

A number of template dependent processes are available to amplify the target sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCR<sup>TM</sup>) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by reference in its entirety. Briefly, in PCR<sup>TM</sup>, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An

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excess of deoxynucleoside triphosphates is added to a reaction mixture along with a DNA polymerase (e.g., Taq polymerase). If the target sequence is present in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction product and the process is repeated. Preferably reverse transcription and PCR<sup>TM</sup> amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

Another method for amplification is the ligase chain reaction (referred to as LCR), disclosed in Eur. Pat. Appl. Publ. No. 320,308 (specifically incorporated herein by reference in its entirety). In LCR, two complementary probe pairs are prepared, and in the presence of the target sequence, each pair will bind to opposite complementary strands of the target such that they abut. In the presence of a ligase, the two probe pairs will link to form a single unit. By temperature cycling, as in PCR<sup>TM</sup>, bound ligated units dissociate from the target and then serve as "target sequences" for ligation of excess probe pairs. U.S. Patent No. 4,883,750, incorporated herein by reference in its entirety, describes an alternative method of amplification similar to LCR for binding probe pairs to a target sequence.

Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No. PCT/US87/00880, incorporated herein by reference in its entirety, may also be used as still another amplification method in the present invention. In this method, a replicative sequence of RNA that has a region complementary to that of a target is added to a sample in the presence of an RNA polymerase. The polymerase will copy the replicative sequence that can then be detected.

An isothermal amplification method, in which restriction endonucleases and ligases are used to achieve the amplification of target molecules that contain nucleotide 5'- $[\alpha$ -thio]triphosphates in one strand of a restriction site (Walker *et al.*, 1992, incorporated

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herein by reference in its entirety), may also be useful in the amplification of nucleic acids in the present invention.

Strand Displacement Amplification (SDA) is another method of carrying out isothermal amplification of nucleic acids which involves multiple rounds of strand displacement and synthesis, *i.e.* nick translation. A similar method, called Repair Chain Reaction (RCR) is another method of amplification which may be useful in the present invention and is involves annealing several probes throughout a region targeted for amplification, followed by a repair reaction in which only two of the four bases are present. The other two bases can be added as biotinylated derivatives for easy detection. A similar approach is used in SDA.

Sequences can also be detected using a cyclic probe reaction (CPR). In CPR, a probe having a 3' and 5' sequences of non-target DNA and an internal or "middle" sequence of the target protein specific RNA is hybridized to DNA which is present in a sample. Upon hybridization, the reaction is treated with RNaseH, and the products of the probe are identified as distinctive products by generating a signal that is released after digestion. The original template is annealed to another cycling probe and the reaction is repeated. Thus, CPR involves amplifying a signal generated by hybridization of a probe to a target gene specific expressed nucleic acid.

Still other amplification methods described in Great Britain Pat. Appl. No. 2 202 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025, each of which is incorporated herein by reference in its entirety, may be used in accordance with the present invention. In the former application, "modified" primers are used in a PCR-like, template and enzyme dependent synthesis. The primers may be modified by labeling with a capture moiety (e.g., biotin) and/or a detector moiety (e.g., enzyme). In the latter application, an excess of labeled probes is added to a sample. In the presence of the target sequence, the probe binds and is cleaved catalytically. After cleavage, the target sequence is released intact to be bound by excess probe. Cleavage of the labeled probe signals the presence of the target sequence.

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Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (Kwoh et al., 1989; PCT Intl. Pat. Appl. Publ. No. WO 88/10315, incorporated herein by reference in its entirety), including nucleic acid sequence based amplification (NASBA) and 3SR. In NASBA, the nucleic acids can be prepared for amplification by standard phenol/chloroform extraction, heat denaturation of a sample, treatment with lysis buffer and minispin columns for isolation of DNA and RNA or guanidinium chloride extraction of RNA. These amplification techniques involve annealing a primer that has sequences specific to the target sequence. Following polymerization, DNA/RNA hybrids are digested with RNase H while double stranded DNA molecules are heat-denatured again. In either case the single stranded DNA is made fully double stranded by addition of second target-specific primer, followed by polymerization. The double stranded DNA molecules are then multiply transcribed by a polymerase such as T7 or SP6. In an isothermal cyclic reaction, the RNAs are reverse transcribed into DNA, and transcribed once again with a polymerase such as T7 or SP6. The resulting products, whether truncated or complete, indicate target-specific sequences.

Eur. Pat. Appl. Publ. No. 329,822, incorporated herein by reference in its entirety, disclose a nucleic acid amplification process involving cyclically synthesizing single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA), which may be used in accordance with the present invention. The ssRNA is a first template for a first primer oligonucleotide, which is elongated by reverse transcriptase (RNA-dependent DNA polymerase). The RNA is then removed from resulting DNA:RNA duplex by the action of ribonuclease H (RNase H, an RNase specific for RNA in a duplex with either DNA or RNA). The resultant ssDNA is a second template for a second primer, which also includes the sequences of an RNA polymerase promoter (exemplified by T7 RNA polymerase) 5' to its homology to its template. This primer is then extended by DNA polymerase (exemplified by the large "Klenow" fragment of *E. coli* DNA polymerase I), resulting as a double-stranded DNA ("dsDNA") molecule, having a sequence identical to that of the original RNA between the primers and having additionally, at one end, a promoter sequence. This promoter sequence can be used by the appropriate RNA polymerase to

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make many RNA copies of the DNA. These copies can then re-enter the cycle leading to very swift amplification. With proper choice of enzymes, this amplification can be done isothermally without addition of enzymes at each cycle. Because of the cyclical nature of this process, the starting sequence can be chosen to be in the form of either DNA or RNA.

PCT Intl. Pat. Appl. Publ. No. WO 89/06700, incorporated herein by reference in its entirety, disclose a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. This scheme is not cyclic; *i.e.* new templates are not produced from the resultant RNA transcripts. Other amplification methods include "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara, 1989) which are well-known to those of skill in the art.

Methods based on ligation of two (or more) oligonucleotides in the presence of nucleic acid having the sequence of the resulting "di-oligonucleotide", thereby amplifying the di-oligonucleotide (Wu and Dean, 1996, incorporated herein by reference in its entirety), may also be used in the amplification of DNA sequences of the present invention.

### **BIOLOGICAL FUNCTIONAL EQUIVALENTS**

Modification and changes may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a polypeptide with desirable characteristics. As mentioned above, it is often desirable to introduce one or more mutations into a specific polynucleotide sequence. In certain circumstances, the resulting encoded polypeptide sequence is altered by this mutation, or in other cases, the sequence of the polypeptide is unchanged by one or more mutations in the encoding polynucleotide.

When it is desirable to alter the amino acid sequence of a polypeptide to create an equivalent, or even an improved, second-generation molecule, the amino acid changes may be achieved by changing one or more of the codons of the encoding DNA sequence, according to Table 1.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated by the inventors that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of their biological utility or activity.

TABLE 1

Amino Acids			Codons					
Alanine	Ala	A	GCA	GCC	GCG	GCU		
Cysteine	Cys	C	UGC	UGU				
Aspartic acid	Asp	D	GAC	GAU				
Glutamic acid	Glu	E	GAA	GAG				
Phenylalanine	Phe	F	UUC	UUU				
Glycine	Gly	G	GGA	GGC	GGG	GGU		
Histidine	His	H	CAC	CAU				
Isoleucine	Ile	I	AUA	AUC	AUU			
Lysine	Lys	K	AAA	AAG				
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU
Methionine	Met	M	AUG					
Asparagine	Asn	N	AAC	AAU				
Proline	Pro	P	CCA	CCC	CCG	CCU		
Glutamine	Gln	Q	CAA	CAG				
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	T	ACA	ACC	ACG	ACU		
Valine	Val	V	GUA	GUC	GUG	GUU		
Tryptophan	Trp	W	UGG					
Tyrosine	Tyr	Y	UAC	UAU				

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been

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assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are within  $\pm 2$  is preferred, those within  $\pm 1$  are particularly preferred, and those within  $\pm 0.5$  are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U. S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein.

As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine ( $\pm$ 3.0); lysine ( $\pm$ 3.0); aspartate ( $\pm$ 3.0  $\pm$ 1); glutamate ( $\pm$ 3.0  $\pm$ 1); serine ( $\pm$ 0.3); asparagine ( $\pm$ 0.2); glutamine ( $\pm$ 0.2); glycine (0); threonine ( $\pm$ 0.4); proline ( $\pm$ 0.5  $\pm$ 1); alanine ( $\pm$ 0.5); histidine ( $\pm$ 0.5); cysteine ( $\pm$ 1.0); methionine ( $\pm$ 1.3); valine ( $\pm$ 1.5); leucine ( $\pm$ 1.8); isoleucine ( $\pm$ 1.8); tyrosine ( $\pm$ 2.3); phenylalanine ( $\pm$ 2.5); tryptophan ( $\pm$ 3.4). It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within  $\pm$ 2 is preferred, those within  $\pm$ 1 are particularly preferred, and those within  $\pm$ 0.5 are even more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their

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hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that take various of the foregoing characteristics into consideration are well known to those of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

In addition, any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

### IN VIVO POLYNUCLEOTIDE DELIVERY TECHNIQUES

In additional embodiments, genetic constructs comprising one or more of the polynucleotides of the invention are introduced into cells *in vivo*. This may be achieved using any of a variety or well known approaches, several of which are outlined below for the purpose of illustration.

## 1. ADENOVIRUS

One of the preferred methods for *in vivo* delivery of one or more nucleic acid sequences involves the use of an adenovirus expression vector. "Adenovirus expression vector" is meant to include those constructs containing adenovirus sequences sufficient to (a) support packaging of the construct and (b) to express a polynucleotide that has been cloned therein in a sense or antisense orientation. Of course, in the context of an antisense construct, expression does not require that the gene product be synthesized.

The expression vector comprises a genetically engineered form of an adenovirus. Knowledge of the genetic organization of adenovirus, a 36 kb, linear, double-stranded DNA virus, allows substitution of large pieces of adenoviral DNA with foreign sequences up to 7 kb (Grunhaus and Horwitz, 1992). In contrast to retrovirus, the adenoviral infection of host cells does not result in chromosomal integration because

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adenoviral DNA can replicate in an episomal manner without potential genotoxicity. Also, adenoviruses are structurally stable, and no genome rearrangement has been detected after extensive amplification. Adenovirus can infect virtually all epithelial cells regardless of their cell cycle stage. So far, adenoviral infection appears to be linked only to mild disease such as acute respiratory disease in humans.

Adenovirus is particularly suitable for use as a gene transfer vector because of its mid-sized genome, ease of manipulation, high titer, wide target-cell range and high infectivity. Both ends of the viral genome contain 100-200 base pair inverted repeats (ITRs), which are *cis* elements necessary for viral DNA replication and packaging. The early (E) and late (L) regions of the genome contain different transcription units that are divided by the onset of viral DNA replication. The E1 region (E1A and E1B) encodes proteins responsible for the regulation of transcription of the viral genome and a few cellular genes. The expression of the E2 region (E2A and E2B) results in the synthesis of the proteins for viral DNA replication. These proteins are involved in DNA replication, late gene expression and host cell shut-off (Renan, 1990). The products of the late genes, including the majority of the viral capsid proteins, are expressed only after significant processing of a single primary transcript issued by the major late promoter (MLP). The MLP, (located at 16.8 m.u.) is particularly efficient during the late phase of infection, and all the mRNA's issued from this promoter possess a 5'-tripartite leader (TPL) sequence which makes them preferred mRNA's for translation.

In a current system, recombinant adenovirus is generated from homologous recombination between shuttle vector and provirus vector. Due to the possible recombination between two proviral vectors, wild-type adenovirus may be generated from this process. Therefore, it is critical to isolate a single clone of virus from an individual plaque and examine its genomic structure.

Generation and propagation of the current adenovirus vectors, which are replication deficient, depend on a unique helper cell line, designated 293, which was transformed from human embryonic kidney cells by Ad5 DNA fragments and constitutively expresses E1 proteins (Graham *et al.*, 1977). Since the E3 region is

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dispensable from the adenovirus genome (Jones and Shenk, 1978), the current adenovirus vectors, with the help of 293 cells, carry foreign DNA in either the E1, the D3 or both regions (Graham and Prevec, 1991). In nature, adenovirus can package approximately 105% of the wild-type genome (Ghosh-Choudhury *et al.*, 1987), providing capacity for about 2 extra kB of DNA. Combined with the approximately 5.5 kB of DNA that is replaceable in the E1 and E3 regions, the maximum capacity of the current adenovirus vector is under 7.5 kB, or about 15% of the total length of the vector. More than 80% of the adenovirus viral genome remains in the vector backbone and is the source of vector-borne cytotoxicity. Also, the replication deficiency of the E1-deleted virus is incomplete. For example, leakage of viral gene expression has been observed with the currently available vectors at high multiplicities of infection (MOI) (Mulligan, 1993).

Helper cell lines may be derived from human cells such as human embryonic kidney cells, muscle cells, hematopoietic cells or other human embryonic mesenchymal or epithelial cells. Alternatively, the helper cells may be derived from the cells of other mammalian species that are permissive for human adenovirus. Such cells include, *e.g.*, Vero cells or other monkey embryonic mesenchymal or epithelial cells. As stated above, the currently preferred helper cell line is 293.

Recently, Racher *et al.* (1995) disclosed improved methods for culturing 293 cells and propagating adenovirus. In one format, natural cell aggregates are grown by inoculating individual cells into 1 liter siliconized spinner flasks (Techne, Cambridge, UK) containing 100-200 ml of medium. Following stirring at 40 rpm, the cell viability is estimated with trypan blue. In another format, Fibra-Cel microcarriers (Bibby Sterlin, Stone, UK) (5 g/l) is employed as follows. A cell inoculum, resuspended in 5 ml of medium, is added to the carrier (50 ml) in a 250 ml Erlenmeyer flask and left stationary, with occasional agitation, for 1 to 4 h. The medium is then replaced with 50 ml of fresh medium and shaking initiated. For virus production, cells are allowed to grow to about 80% confluence, after which time the medium is replaced (to 25% of the final volume) and adenovirus added at an MOI of 0.05. Cultures are left stationary overnight, following which the volume is increased to 100% and shaking commenced for another 72 h.

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Other than the requirement that the adenovirus vector be replication defective, or at least conditionally defective, the nature of the adenovirus vector is not believed to be crucial to the successful practice of the invention. The adenovirus may be of any of the 42 different known serotypes or subgroups A-F. Adenovirus type 5 of subgroup C is the preferred starting material in order to obtain a conditional replication-defective adenovirus vector for use in the present invention, since Adenovirus type 5 is a human adenovirus about which a great deal of biochemical and genetic information is known, and it has historically been used for most constructions employing adenovirus as a vector.

As stated above, the typical vector according to the present invention is replication defective and will not have an adenovirus E1 region. Thus, it will be most convenient to introduce the polynucleotide encoding the gene of interest at the position from which the E1-coding sequences have been removed. However, the position of insertion of the construct within the adenovirus sequences is not critical to the invention. The polynucleotide encoding the gene of interest may also be inserted in lieu of the deleted E3 region in E3 replacement vectors as described by Karlsson *et al.* (1986) or in the E4 region where a helper cell line or helper virus complements the E4 defect.

Adenovirus is easy to grow and manipulate and exhibits broad host range in vitro and in vivo. This group of viruses can be obtained in high titers, e.g.,  $10^9$ - $10^{11}$  plaque-forming units per ml, and they are highly infective. The life cycle of adenovirus does not require integration into the host cell genome. The foreign genes delivered by adenovirus vectors are episomal and, therefore, have low genotoxicity to host cells. No side effects have been reported in studies of vaccination with wild-type adenovirus (Couch et al., 1963; Top et al., 1971), demonstrating their safety and therapeutic potential as in vivo gene transfer vectors.

Adenovirus vectors have been used in eukaryotic gene expression (Levrero et al., 1991; Gomez-Foix et al., 1992) and vaccine development (Grunhaus and Horwitz, 1992; Graham and Prevec, 1992). Recently, animal studies suggested that recombinant adenovirus could be used for gene therapy (Stratford-Perricaudet and Perricaudet, 1991; Stratford-Perricaudet et al., 1990; Rich et al., 1993). Studies in administering recombinant

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adenovirus to different tissues include trachea instillation (Rosenfeld *et al.*, 1991; Rosenfeld *et al.*, 1992), muscle injection (Ragot *et al.*, 1993), peripheral intravenous injections (Herz and Gerard, 1993) and stereotactic inoculation into the brain (Le Gal La Salle *et al.*, 1993).

# 5 2. Retroviruses

The retroviruses are a group of single-stranded RNA viruses characterized by an ability to convert their RNA to double-stranded DNA in infected cells by a process of reverse-transcription (Coffin, 1990). The resulting DNA then stably integrates into cellular chromosomes as a provirus and directs synthesis of viral proteins. The integration results in the retention of the viral gene sequences in the recipient cell and its descendants. The retroviral genome contains three genes, gag, pol, and env that code for capsid proteins, polymerase enzyme, and envelope components, respectively. A sequence found upstream from the gag gene contains a signal for packaging of the genome into virions. Two long terminal repeat (LTR) sequences are present at the 5' and 3' ends of the viral genome. These contain strong promoter and enhancer sequences and are also required for integration in the host cell genome (Coffin, 1990).

In order to construct a retroviral vector, a nucleic acid encoding one or more oligonucleotide or polynucleotide sequences of interest is inserted into the viral genome in the place of certain viral sequences to produce a virus that is replication-defective. In order to produce virions, a packaging cell line containing the gag, pol, and env genes but without the LTR and packaging components is constructed (Mann *et al.*, 1983). When a recombinant plasmid containing a cDNA, together with the retroviral LTR and packaging sequences is introduced into this cell line (by calcium phosphate precipitation for example), the packaging sequence allows the RNA transcript of the recombinant plasmid to be packaged into viral particles, which are then secreted into the culture media (Nicolas and Rubenstein, 1988; Temin, 1986; Mann *et al.*, 1983). The media containing the recombinant retroviruses is then collected, optionally concentrated, and used for gene

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transfer. Retroviral vectors are able to infect a broad variety of cell types. However, integration and stable expression require the division of host cells (Paskind *et al.*, 1975).

A novel approach designed to allow specific targeting of retrovirus vectors was recently developed based on the chemical modification of a retrovirus by the chemical addition of lactose residues to the viral envelope. This modification could permit the specific infection of hepatocytes *via* sialoglycoprotein receptors.

A different approach to targeting of recombinant retroviruses was designed in which biotinylated antibodies against a retroviral envelope protein and against a specific cell receptor were used. The antibodies were coupled *via* the biotin components by using streptavidin (Roux *et al.*, 1989). Using antibodies against major histocompatibility complex class I and class II antigens, they demonstrated the infection of a variety of human cells that bore those surface antigens with an ecotropic virus *in vitro* (Roux *et al.*, 1989).

#### 3. ADENO-ASSOCIATED VIRUSES

AAV (Ridgeway, 1988; Hermonat and Muzycska, 1984) is a parovirus, discovered as a contamination of adenoviral stocks. It is a ubiquitous virus (antibodies are present in 85% of the US human population) that has not been linked to any disease. It is also classified as a dependovirus, because its replications is dependent on the presence of a helper virus, such as adenovirus. Five serotypes have been isolated, of which AAV-2 is the best characterized. AAV has a single-stranded linear DNA that is encapsidated into capsid proteins VP1, VP2 and VP3 to form an icosahedral virion of 20 to 24 nm in diameter (Muzyczka and McLaughlin, 1988).

The AAV DNA is approximately 4.7 kilobases long. It contains two open reading frames and is flanked by two ITRs. There are two major genes in the AAV genome: *rep* and *cap*. The *rep* gene codes for proteins responsible for viral replications, whereas *cap* codes for capsid protein VP1-3. Each ITR forms a T-shaped hairpin structure. These terminal repeats are the only essential *cis* components of the AAV for chromosomal integration. Therefore, the AAV can be used as a vector with all viral coding sequences removed and replaced by the cassette of genes for delivery. Three viral

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promoters have been identified and named p5, p19, and p40, according to their map position. Transcription from p5 and p19 results in production of rep proteins, and transcription from p40 produces the capsid proteins (Hermonat and Muzyczka, 1984).

There are several factors that prompted researchers to study the possibility of using rAAV as an expression vector. One is that the requirements for delivering a gene to integrate into the host chromosome are surprisingly few. It is necessary to have the 145-bp ITRs, which are only 6% of the AAV genome. This leaves room in the vector to assemble a 4.5-kb DNA insertion. While this carrying capacity may prevent the AAV from delivering large genes, it is amply suited for delivering the antisense constructs of the present invention.

AAV is also a good choice of delivery vehicles due to its safety. There is a relatively complicated rescue mechanism: not only wild type adenovirus but also AAV genes are required to mobilize rAAV. Likewise, AAV is not pathogenic and not associated with any disease. The removal of viral coding sequences minimizes immune reactions to viral gene expression, and therefore, rAAV does not evoke an inflammatory response.

## 4. OTHER VIRAL VECTORS AS EXPRESSION CONSTRUCTS

Other viral vectors may be employed as expression constructs in the present invention for the delivery of oligonucleotide or polynucleotide sequences to a host cell. Vectors derived from viruses such as vaccinia virus (Ridgeway, 1988; Coupar *et al.*, 1988), lentiviruses, polio viruses and herpes viruses may be employed. They offer several attractive features for various mammalian cells (Friedmann, 1989; Ridgeway, 1988; Coupar *et al.*, 1988; Horwich *et al.*, 1990).

With the recent recognition of defective hepatitis B viruses, new insight was gained into the structure-function relationship of different viral sequences. *In vitro* studies showed that the virus could retain the ability for helper-dependent packaging and reverse transcription despite the deletion of up to 80% of its genome (Horwich *et al.*, 1990). This suggested that large portions of the genome could be replaced with foreign genetic material. The hepatotropism and persistence (integration) were particularly attractive

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properties for liver-directed gene transfer. Chang et al. (1991) introduced the chloramphenical acetyltransferase (CAT) gene into duck hepatitis B virus genome in the place of the polymerase, surface, and pre-surface coding sequences. It was cotransfected with wild-type virus into an avian hepatoma cell line. Culture media containing high titers of the recombinant virus were used to infect primary duckling hepatocytes. Stable CAT gene expression was detected for at least 24 days after transfection (Chang et al., 1991).

# 5. Non-viral vectors

In order to effect expression of the oligonucleotide or polynucleotide sequences of the present invention, the expression construct must be delivered into a cell. This delivery may be accomplished *in vitro*, as in laboratory procedures for transforming cells lines, or *in vivo* or *ex vivo*, as in the treatment of certain disease states. As described above, one preferred mechanism for delivery is *via* viral infection where the expression construct is encapsulated in an infectious viral particle.

Once the expression construct has been delivered into the cell the nucleic acid encoding the desired oligonucleotide or polynucleotide sequences may be positioned and expressed at different sites. In certain embodiments, the nucleic acid encoding the construct may be stably integrated into the genome of the cell. This integration may be in the specific location and orientation *via* homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the nucleic acid may be stably maintained in the cell as a separate, episomal segment of DNA. Such nucleic acid segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. How the expression construct is delivered to a cell and where in the cell the nucleic acid remains is dependent on the type of expression construct employed.

In certain embodiments of the invention, the expression construct comprising one or more oligonucleotide or polynucleotide sequences may simply consist of naked recombinant DNA or plasmids. Transfer of the construct may be performed by any of the methods mentioned above which physically or chemically permeabilize the cell

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membrane. This is particularly applicable for transfer *in vitro* but it may be applied to *in vivo* use as well. Dubensky *et al.* (1984) successfully injected polyomavirus DNA in the form of calcium phosphate precipitates into liver and spleen of adult and newborn mice demonstrating active viral replication and acute infection. Benvenisty and Reshef (1986) also demonstrated that direct intraperitoneal injection of calcium phosphate-precipitated plasmids results in expression of the transfected genes. It is envisioned that DNA encoding a gene of interest may also be transferred in a similar manner *in vivo* and express the gene product.

Another embodiment of the invention for transferring a naked DNA expression construct into cells may involve particle bombardment. This method depends on the ability to accelerate DNA-coated microprojectiles to a high velocity allowing them to pierce cell membranes and enter cells without killing them (Klein *et al.*, 1987). Several devices for accelerating small particles have been developed. One such device relies on a high voltage discharge to generate an electrical current, which in turn provides the motive force (Yang *et al.*, 1990). The microprojectiles used have consisted of biologically inert substances such as tungsten or gold beads.

Selected organs including the liver, skin, and muscle tissue of rats and mice have been bombarded *in vivo* (Yang *et al.*, 1990; Zelenin *et al.*, 1991). This may require surgical exposure of the tissue or cells, to eliminate any intervening tissue between the gun and the target organ, *i.e. ex vivo* treatment. Again, DNA encoding a particular gene may be delivered *via* this method and still be incorporated by the present invention.

#### ANTISENSE OLIGONUCLEOTIDES

The end result of the flow of genetic information is the synthesis of protein. DNA is transcribed by polymerases into messenger RNA and translated on the ribosome to yield a folded, functional protein. Thus there are several steps along the route where protein synthesis can be inhibited. The native DNA segment coding for a polypeptide described herein, as all such mammalian DNA strands, has two strands: a sense strand and an antisense strand held together by hydrogen bonding. The messenger RNA coding for

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polypeptide has the same nucleotide sequence as the sense DNA strand except that the DNA thymidine is replaced by uridine. Thus, synthetic antisense nucleotide sequences will bind to a mRNA and inhibit expression of the protein encoded by that mRNA.

The targeting of antisense oligonucleotides to mRNA is thus one mechanism to shut down protein synthesis, and, consequently, represents a powerful and targeted therapeutic approach. For example, the synthesis of polygalactauronase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829, each specifically incorporated herein by reference in its entirety). Further, examples of antisense inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal GABA<sub>A</sub> receptor and human EGF (Jaskulski *et al.*, 1988; Vasanthakumar and Ahmed, 1989; Peris *et al.*, 1998; U. S. Patent 5,801,154; U. S. Patent 5,789,573; U. S. Patent 5,718,709 and U. S. Patent 5,610,288, each specifically incorporated herein by reference in its entirety). Antisense constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683, each specifically incorporated herein by reference in its entirety).

embodiments, provides invention Therefore, exemplary the in oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a oligonucleotides modified DNAs comprising third embodiment, the are phosphorothioated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In each case, preferred compositions comprise a sequence region that is complementary, and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein.

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Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence (*i.e.* in these illustrative examples the rat and human sequences) and determination of secondary structure, T<sub>m</sub>, binding energy, relative stability, and antisense compositions were selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell.

Highly preferred target regions of the mRNA, are those which are at or near the AUG translation initiation codon, and those sequences which were substantially complementary to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations were performed using v.4 of the OLIGO primer analysis software (Rychlik, 1997) and the BLASTN 2.0.5 algorithm software (Altschul *et al.*, 1997).

The use of an antisense delivery method employing a short peptide vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*, 1997). It has been demonstrated that several molecules of the MPG peptide coat the antisense oligonucleotides and can be delivered into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the oligonucleotide to nuclease and the ability to cross the plasma membrane (Morris *et al.*, 1997).

## **RIBOZYMES**

Although proteins traditionally have been used for catalysis of nucleic acids, another class of macromolecules has emerged as useful in this endeavor. Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cech, 1987; Gerlach *et al.*, 1987; Forster and Symons, 1987). For example, a large number of ribozymes accelerate phosphoester transfer reactions with a high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech *et* 

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al., 1981; Michel and Westhof, 1990; Reinhold-Hurek and Shub, 1992). This specificity has been attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

Ribozyme catalysis has primarily been observed as part of sequence-specific cleavage/ligation reactions involving nucleic acids (Joyce, 1989; Cech *et al.*, 1981). For example, U. S. Patent No. 5,354,855 (specifically incorporated herein by reference) reports that certain ribozymes can act as endonucleases with a sequence specificity greater than that of known ribonucleases and approaching that of the DNA restriction enzymes. Thus, sequence-specific ribozyme-mediated inhibition of gene expression may be particularly suited to therapeutic applications (Scanlon *et al.*, 1991; Sarver *et al.*, 1990). Recently, it was reported that ribozymes elicited genetic changes in some cells lines to which they were applied; the altered genes included the oncogenes H-*ras*, c-*fos* and genes of HIV. Most of this work involved the modification of a target mRNA, based on a specific mutant codon that is cleaved by a specific ribozyme.

Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of a ribozyme is advantageous over many technologies, such as antisense technology (where a nucleic acid molecule simply binds to

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a nucleic acid target to block its translation) since the concentration of ribozyme necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action (Woolf *et al.*, 1992). Thus, the specificity of action of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis δ virus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or Neurospora VS RNA motif. Examples of hammerhead motifs are described by Rossi et al. (1992). Examples of hairpin motifs are described by Hampel et al. (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz (1989), Hampel et al. (1990) and U. S. Patent 5,631,359 (specifically incorporated herein by reference). An example of the hepatitis  $\delta$  virus motif is described by Perrotta and Been (1992); an example of the RNaseP motif is described by Guerrier-Takada et al. (1983); Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, 1990; Saville and Collins, 1991; Collins and Olive, 1993); and an example of the Group I intron is described in (U. S. Patent 4,987,071, specifically incorporated herein by reference). All that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

In certain embodiments, it may be important to produce enzymatic cleaving agents which exhibit a high degree of specificity for the RNA of a desired target, such as

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one of the sequences disclosed herein. The enzymatic nucleic acid molecule is preferably targeted to a highly conserved sequence region of a target mRNA. Such enzymatic nucleic acid molecules can be delivered exogenously to specific cells as required. Alternatively, the ribozymes can be expressed from DNA or RNA vectors that are delivered to specific cells.

Small enzymatic nucleic acid motifs (e.g., of the hammerhead or the hairpin structure) may also be used for exogenous delivery. The simple structure of these molecules increases the ability of the enzymatic nucleic acid to invade targeted regions of the mRNA structure. Alternatively, catalytic RNA molecules can be expressed within cells from eukaryotic promoters (e.g., Scanlon et al., 1991; Kashani-Sabet et al., 1992; Dropulic et al., 1992; Weerasinghe et al., 1991; Ojwang et al., 1992; Chen et al., 1992; Sarver et al., 1990). Those skilled in the art realize that any ribozyme can be expressed in eukaryotic cells from the appropriate DNA vector. The activity of such ribozymes can be augmented by their release from the primary transcript by a second ribozyme (Int. Pat. Appl. Publ. No. WO 93/23569, and Int. Pat. Appl. Publ. No. WO 94/02595, both hereby incorporated by reference; Ohkawa et al., 1992; Taira et al., 1991; and Ventura et al., 1993).

Ribozymes may be added directly, or can be complexed with cationic lipids, lipid complexes, packaged within liposomes, or otherwise delivered to target cells. The RNA or RNA complexes can be locally administered to relevant tissues *ex vivo*, or *in vivo* through injection, aerosol inhalation, infusion pump or stent, with or without their incorporation in biopolymers.

Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as described. Such ribozymes can also be optimized for delivery. While specific examples are provided, those in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Hammerhead or hairpin ribozymes may be individually analyzed by computer folding (Jaeger et al., 1989) to assess whether the ribozyme sequences fold into

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the appropriate secondary structure. Those ribozymes with unfavorable intramolecular interactions between the binding arms and the catalytic core are eliminated from consideration. Varying binding arm lengths can be chosen to optimize activity. Generally, at least 5 or so bases on each arm are able to bind to, or otherwise interact with, the target RNA.

Ribozymes of the hammerhead or hairpin motif may be designed to anneal to various sites in the mRNA message, and can be chemically synthesized. The method of synthesis used follows the procedure for normal RNA synthesis as described in Usman *et al.* (1987) and in Scaringe *et al.* (1990) and makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. Average stepwise coupling yields are typically >98%. Hairpin ribozymes may be synthesized in two parts and annealed to reconstruct an active ribozyme (Chowrira and Burke, 1992). Ribozymes may be modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-flouro, 2'-o-methyl, 2'-H (for a review see *e.g.*, Usman and Cedergren, 1992). Ribozymes may be purified by gel electrophoresis using general methods or by high pressure liquid chromatography and resuspended in water.

Ribozyme activity can be optimized by altering the length of the ribozyme binding arms, or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see *e.g.*, Int. Pat. Appl. Publ. No. WO 92/07065; Perrault *et al*, 1990; Pieken *et al.*, 1991; Usman and Cedergren, 1992; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

Sullivan et al. (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be

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administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each specifically incorporated herein by reference.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, etc.) present nearby. Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990; Gao and Huang, 1993; Lieber et al., 1993; Zhou et al., 1990). Ribozymes expressed from such promoters can function in mammalian cells (e.g. Kashani-Saber et al., 1992; Ojwang et al., 1992; Chen et al., 1992; Yu et al., 1993; L'Huillier et al., 1992; Lisziewicz et al., 1993). Such transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral, semliki forest virus, sindbis virus vectors).

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Ribozymes may be used as diagnostic tools to examine genetic drift and mutations within diseased cells. They can also be used to assess levels of the target RNA molecule. The close relationship between ribozyme activity and the structure of the target RNA allows the detection of mutations in any region of the molecule which alters the basepairing and three-dimensional structure of the target RNA. By using multiple ribozymes, one may map nucleotide changes which are important to RNA structure and function in vitro, as well as in cells and tissues. Cleavage of target RNAs with ribozymes may be used to inhibit gene expression and define the role (essentially) of specified gene products in the progression of disease. In this manner, other genetic targets may be defined as important mediators of the disease. These studies will lead to better treatment of the disease progression by affording the possibility of combinational therapies (e.g., multiple ribozymes targeted to different genes, ribozymes coupled with known small molecule inhibitors, or intermittent treatment with combinations of ribozymes and/or other chemical or biological molecules). Other in vitro uses of ribozymes are well known in the art, and include detection of the presence of mRNA associated with an IL-5 related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a ribozyme using standard methodology.

## PEPTIDE NUCLEIC ACIDS

In certain embodiments, the inventors contemplate the use of peptide nucleic acids (PNAs) in the practice of the methods of the invention. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, 1997). PNA is able to be utilized in a number methods that traditionally have used RNA or DNA. Often PNA sequences perform better in techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided by Corey (1997) and is incorporated herein by reference. As such, in certain embodiments, one may prepare PNA sequences that are complementary to one or more portions of the ACE mRNA sequence, and such PNA compositions may be used to regulate, alter,

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decrease, or reduce the translation of ACE-specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

PNAs have 2-aminoethyl-glycine linkages replacing the normal phosphodiester backbone of DNA (Nielsen *et al.*, 1991; Hanvey *et al.*, 1992; Hyrup and Nielsen, 1996; Neilsen, 1996). This chemistry has three important consequences: firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a stereoselective synthesis; and thirdly, PNA synthesis uses standard Boc (Dueholm *et al.*, 1994) or Fmoc (Thomson *et al.*, 1995) protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used (Christensen *et al.*, 1995).

PNA monomers or ready-made oligomers are commercially available from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or Fmoc protocols are straightforward using manual or automated protocols (Norton *et al.*, 1995). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will depend on the properties of the chosen sequence. For example, while in theory PNAs can incorporate any combination of nucleotide bases, the presence of adjacent purines can lead to deletions of one or more residues in the product. In expectation of this difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed by the purification of PNAs by reverse-phase high-pressure liquid chromatography (Norton *et al.*, 1995) providing yields and purity of product similar to those observed during the synthesis of peptides.

Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or for specific

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functional requirements. Once synthesized, the identity of PNAs and their derivatives can be confirmed by mass spectrometry. Several studies have made and utilized modifications of PNAs (Norton et al., 1995; Haaima et al., 1996; Stetsenko et al., 1996; Petersen et al., 1995; Ulmann et al., 1996; Koch et al., 1995; Orum et al., 1995; Footer et al., 1996; Griffith et al., 1995; Kremsky et al., 1996; Pardridge et al., 1995; Boffa et al., 1995; Landsdorp et al., 1996; Gambacorti-Passerini et al., 1996; Armitage et al., 1997; Seeger et al., 1997; Ruskowski et al., 1997). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in diagnostics, modulating protein in organisms, and treatment of conditions susceptible to therapeutics.

In contrast to DNA and RNA, which contain negatively charged linkages, the PNA backbone is neutral. In spite of this dramatic alteration, PNAs recognize complementary DNA and RNA by Watson-Crick pairing (Egholm *et al.*, 1993), validating the initial modeling by Nielsen *et al.* (1991). PNAs lack 3' to 5' polarity and can bind in either parallel or antiparallel fashion, with the antiparallel mode being preferred (Egholm *et al.*, 1993).

Hybridization of DNA oligonucleotides to DNA and RNA is destabilized by electrostatic repulsion between the negatively charged phosphate backbones of the complementary strands. By contrast, the absence of charge repulsion in PNA-DNA or PNA-RNA duplexes increases the melting temperature ( $T_{\rm m}$ ) and reduces the dependence of  $T_{\rm m}$  on the concentration of mono- or divalent cations (Nielsen *et al.*, 1991). The enhanced rate and affinity of hybridization are significant because they are responsible for the surprising ability of PNAs to perform strand invasion of complementary sequences within relaxed double-stranded DNA. In addition, the efficient hybridization at inverted repeats suggests that PNAs can recognize secondary structure effectively within double-stranded DNA. Enhanced recognition also occurs with PNAs immobilized on surfaces, and Wang *et al.*, have shown that support-bound PNAs can be used to detect hybridization events (Wang *et al.*, 1996).

One might expect that tight binding of PNAs to complementary sequences would also increase binding to similar (but not identical) sequences, reducing the sequence

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specificity of PNA recognition. As with DNA hybridization, however, selective recognition can be achieved by balancing oligomer length and incubation temperature. Moreover, selective hybridization of PNAs is encouraged by PNA-DNA hybridization being less tolerant of base mismatches than DNA-DNA hybridization. For example, a single mismatch within a 16 bp PNA-DNA duplex can reduce the  $T_{\rm m}$  by up to 15°C (Egholm *et al.*, 1993). This high level of discrimination has allowed the development of several PNA-based strategies for the analysis of point mutations (Wang *et al.*, 1996; Carlsson *et al.*, 1996; Thiede *et al.*, 1996; Webb and Hurskainen, 1996; Perry-O'Keefe *et al.*, 1996).

High-affinity binding provides clear advantages for molecular recognition and the development of new applications for PNAs. For example, 11-13 nucleotide PNAs inhibit the activity of telomerase, a ribonucleo-protein that extends telomere ends using an essential RNA template, while the analogous DNA oligomers do not (Norton *et al.*, 1996).

Neutral PNAs are more hydrophobic than analogous DNA oligomers, and this can lead to difficulty solubilizing them at neutral pH, especially if the PNAs have a high purine content or if they have the potential to form secondary structures. Their solubility can be enhanced by attaching one or more positive charges to the PNA termini (Nielsen *et al.*, 1991).

Findings by Allfrey and colleagues suggest that strand invasion will occur spontaneously at sequences within chromosomal DNA (Boffa *et al.*, 1995; Boffa *et al.*, 1996). These studies targeted PNAs to triplet repeats of the nucleotides CAG and used this recognition to purify transcriptionally active DNA (Boffa *et al.*, 1995) and to inhibit transcription (Boffa *et al.*, 1996). This result suggests that if PNAs can be delivered within cells then they will have the potential to be general sequence-specific regulators of gene expression. Studies and reviews concerning the use of PNAs as antisense and anti-gene agents include Nielsen *et al.* (1993b), Hanvey *et al.* (1992), and Good and Nielsen (1997). Koppelhus *et al.* (1997) have used PNAs to inhibit HIV-1 inverse transcription, showing that PNAs may be used for antiviral therapies.

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Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (1993) and Jensen *et al.* (1997). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide, measuring the relative binding kinetics and stoichiometry. Similar types of measurements were made by Jensen *et al.* using BIAcore<sup>TM</sup> technology.

Other applications of PNAs include use in DNA strand invasion (Nielsen et al., 1991), antisense inhibition (Hanvey et al., 1992), mutational analysis (Orum et al., 1993), enhancers of transcription (Mollegaard et al., 1994), nucleic acid purification (Orum et al., 1995), isolation of transcriptionally active genes (Boffa et al., 1995), blocking of transcription factor binding (Vickers et al., 1995), genome cleavage (Veselkov et al., 1996), biosensors (Wang et al., 1996), in situ hybridization (Thisted et al., 1996), and in a alternative to Southern blotting (Perry-O'Keefe, 1996).

#### POLYPEPTIDE COMPOSITIONS

The present invention, in other aspects, provides polypeptide compositions. Generally, a polypeptide of the invention will be an isolated polypeptide (or an epitope, variant, or active fragment thereof) derived from a mammalian species. Preferably, the polypeptide is encoded by a polynucleotide sequence disclosed herein or a sequence which hybridizes under moderately stringent conditions to a polynucleotide sequence disclosed herein. Alternatively, the polypeptide may be defined as a polypeptide which comprises a contiguous amino acid sequence from an amino acid sequence disclosed herein, or which polypeptide comprises an entire amino acid sequence disclosed herein.

In the present invention, a polypeptide composition is also understood to comprise one or more polypeptides that are immunologically reactive with antibodies generated against a polypeptide of the invention, particularly a polypeptide having the amino acid sequence disclosed in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 706-708, 775, 776, 778 and 780, or active fragments, variants or biological functional equivalents thereof.

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Likewise, a polypeptide composition of the present invention is understood to comprise one or more polypeptides that are capable of eliciting antibodies that are immunologically reactive with one or more polypeptides encoded by one or more contiguous nucleic acid sequences contained in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789, or to active fragments, or to variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency. Particularly illustrative polypeptides include the amino acid sequence disclosed in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 706-708, 775, 776, 778 and 780.

As used herein, an active fragment of a polypeptide includes a whole or a portion of a polypeptide which is modified by conventional techniques, *e.g.*, mutagenesis, or by addition, deletion, or substitution, but which active fragment exhibits substantially the same structure function, antigenicity, etc., as a polypeptide as described herein.

In certain illustrative embodiments, the polypeptides of the invention will comprise at least an immunogenic portion of a prostate-specific protein or a variant thereof, as described herein. As noted above, a "prostate-specific protein" is a protein that is expressed by prostate cells. Proteins that are prostate-specific proteins also react detectably within an immunoassay (such as an ELISA) with antisera from a patient with prostate cancer. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of a protein that is recognized (*i.e.*, specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of a prostate-specific protein or a variant thereof. Certain preferred immunogenic portions

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include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other preferred immunogenic portions may contain a small N- and/or C-terminal deletion (e.g., 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, Fundamental Immunology, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (i.e., they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well known techniques. An immunogenic portion of a native prostate-specific protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (e.g., in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, <sup>125</sup>I-labeled Protein A.

As noted above, a composition may comprise a variant of a native prostate-specific protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native prostate-specific protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with antigen-specific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than

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50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (e.g., 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

Polypeptide variants encompassed by the present invention include those exhibiting at least about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity (determined as described above) to the polypeptides disclosed herein.

Preferably, a variant contains conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine. phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the

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deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (*e.g.*, poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast, and higher eukaryotic cells, such as mammalian cells and plant cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having less than about 100 amino acids, and generally less than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. *See* Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from

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suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of

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hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea *et al.*, *Gene 40*:39-46, 1985; Murphy *et al.*, *Proc. Natl. Acad. Sci. USA 83*:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided. Such proteins comprise a polypeptide as described herein together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. New Engl. J. Med., 336:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (e.g., the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in E. coli (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein

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from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10*:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

### **BINDING AGENTS**

The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to a prostate-specific protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to a prostate-specific protein if it reacts at a detectable level (within, for example, an

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ELISA) with a prostate-specific protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10<sup>3</sup> L/mol. The binding constant may be determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as prostate cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a prostate-specific protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (e.g., blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of

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monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, Eur. J. Immunol. 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the

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yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988) and digested by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include <sup>90</sup>Y, <sup>123</sup>I, <sup>125</sup>I, <sup>131</sup>I, <sup>186</sup>Re, <sup>188</sup>Re, <sup>211</sup>At, and <sup>212</sup>Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

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Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell *et al.* 

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (e.g., U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (e.g., U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (e.g., U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (e.g., U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled

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directly to an antibody molecule, or linkers that provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

## 20 T CELLS

Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for a prostate-specific protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the Isolex<sup>TM</sup> System, available from Nexell Therapeutics, Inc. (Irvine, CA; see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243).

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Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a prostate-specific polypeptide, polynucleotide encoding a prostate-specific polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, a prostate-specific polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a prostate-specific polypeptide if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., Cancer Res. 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (e.g., by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a prostate-specific polypeptide (100 ng/ml - 100 µg/ml, preferably 200 ng/ml - 25 µg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-γ) is indicative of T cell activation (see Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a prostate-specific polypeptide, polynucleotide or polypeptide-expressing APC may be CD4<sup>+</sup> and/or CD8<sup>+</sup>. prostate-specific protein-specific T cells may be expanded using standard techniques.

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Within preferred embodiments, the T cells are derived from a patient, a related donor or an unrelated donor, and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4<sup>+</sup> or CD8<sup>+</sup> T cells that proliferate in response to a prostate-specific polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a prostate-specific polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a prostate-specific polypeptide. Alternatively, one or more T cells that proliferate in the presence of a prostate-specific protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

#### PHARMACEUTICAL COMPOSITIONS

In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell and/or antibody compositions disclosed herein in pharmaceutically-acceptable solutions for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy.

It will also be understood that, if desired, the nucleic acid segment, RNA, DNA or PNA compositions that express a polypeptide as disclosed herein may be administered in combination with other agents as well, such as, e.g., other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is virtually no limit to other components that may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or host tissues. The compositions may thus be delivered along with various other agents as required in the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as described herein. Likewise, such compositions may further comprise substituted or derivatized RNA or DNA compositions.

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Formulation of pharmaceutically-acceptable excipients and carrier solutions is well-known to those of skill in the art, as is the development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including *e.g.*, oral, parenteral, intravenous, intranasal, and intramuscular administration and formulation.

## 1. ORAL DELIVERY

In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (Mathiowitz et al., 1997; Hwang et al., 1998; U. S. Patent 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451, each specifically incorporated herein by reference in its entirety). The tablets, troches, pills, capsules and the like may also contain the following: a binder, as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. A syrup of elixir may contain the active compound sucrose as a sweetening agent methyl and propylparabens as preservatives, a dye and flavoring, such as cherry or orange Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition,

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the active compounds may be incorporated into sustained-release preparation and formulations.

Typically, these formulations may contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of active compound(s) in each therapeutically useful composition may be prepared is such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

For oral administration the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash, dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. For example, a mouthwash may be prepared incorporating the active ingredient in the required amount in an appropriate solvent, such as a sodium borate solution (Dobell's Solution). Alternatively, the active ingredient may be incorporated into an oral solution such as one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants. Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the tongue or otherwise dissolved in the mouth.

### 2. INJECTABLE DELIVERY

In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even intraperitoneally as described in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U. S. Patent 5,399,363 (each specifically incorporated herein by reference in its entirety).

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Solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (U. S. Patent 5,466,468, specifically incorporated herein by reference in its entirety). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or

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injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject. Moreover, for human administration, preparations should meet sterility, pyrogenicity, and the general safety and purity standards as required by FDA Office of Biologics standards.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The compositions disclosed herein may be formulated in a neutral or salt form. Pharmaceutically-acceptable salts, include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms such as injectable solutions, drug-release capsules, and the like.

As used herein, "carrier" includes any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption

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delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

The phrase "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human. The preparation of an aqueous composition that contains a protein as an active ingredient is well understood in the art. Typically, such compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection can also be prepared. The preparation can also be emulsified.

# 3. NASAL DELIVERY

In certain embodiments, the pharmaceutical compositions may be delivered by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the lungs *via* nasal aerosol sprays has been described *e.g.*, in U. S. Patent 5,756,353 and U. S. Patent 5,804,212 (each specifically incorporated herein by reference in its entirety). Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga *et al.*, 1998) and lysophosphatidylglycerol compounds (U. S. Patent 5,725,871, specifically incorporated herein by reference in its entirety) are also well-known in the pharmaceutical arts. Likewise, transmucosal drug delivery in the form of a polytetrafluoroetheylene support matrix is described in U. S. Patent 5,780,045 (specifically incorporated herein by reference in its entirety).

# 4. LIPOSOME-, NANOCAPSULE-, AND MICROPARTICLE-MEDIATED DELIVERY

In certain embodiments, the inventors contemplate the use of liposomes, nanocapsules, microparticles, microspheres, lipid particles, vesicles, and the like, for the introduction of the compositions of the present invention into suitable host cells. In

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particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like.

Such formulations may be preferred for the introduction of pharmaceutically-acceptable formulations of the nucleic acids or constructs disclosed herein. The formation and use of liposomes is generally known to those of skill in the art (see for example, Couvreur et al., 1977; Couvreur, 1988; Lasic, 1998; which describes the use of liposomes and nanocapsules in the targeted antibiotic therapy for intracellular bacterial infections and diseases). Recently, liposomes were developed with improved serum stability and circulation half-times (Gabizon and Papahadjopoulos, 1988; Allen and Choun, 1987; U. S. Patent 5,741,516, specifically incorporated herein by reference in its entirety). Further, various methods of liposome and liposome like preparations as potential drug carriers have been reviewed (Takakura, 1998; Chandran et al., 1997; Margalit, 1995; U. S. Patent 5,567,434; U. S. Patent 5,552,157; U. S. Patent 5,565,213; U. S. Patent 5,738,868 and U. S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

Liposomes have been used successfully with a number of cell types that are normally resistant to transfection by other procedures including T cell suspensions, primary hepatocyte cultures and PC 12 cells (Renneisen *et al.*, 1990; Muller *et al.*, 1990). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery systems. Liposomes have been used effectively to introduce genes, drugs (Heath and Martin, 1986; Heath *et al.*, 1986; Balazsovits *et al.*, 1989; Fresta and Puglisi, 1996), radiotherapeutic agents (Pikul *et al.*, 1987), enzymes (Imaizumi *et al.*, 1990a; Imaizumi *et al.*, 1990b), viruses (Faller and Baltimore, 1984), transcription factors and allosteric effectors (Nicolau and Gersonde, 1979) into a variety of cultured cell lines and animals. In addition, several successful clinical trails examining the effectiveness of liposome-mediated drug delivery have been completed (Lopez-Berestein *et al.*, 1985a; 1985b; Coune, 1988; Sculier *et al.*, 1988). Furthermore, several studies suggest that the use of

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liposomes is not associated with autoimmune responses, toxicity or gonadal localization after systemic delivery (Mori and Fukatsu, 1992).

Liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs). MLVs generally have diameters of from 25 nm to 4  $\mu$ m. Sonication of MLVs results in the formation of small unilamellar vesicles (SUVs) with diameters in the range of 200 to 500 Å, containing an aqueous solution in the core.

Liposomes bear resemblance to cellular membranes and are contemplated for use in connection with the present invention as carriers for the peptide compositions. They are widely suitable as both water- and lipid-soluble substances can be entrapped, *i.e.* in the aqueous spaces and within the bilayer itself, respectively. It is possible that the drugbearing liposomes may even be employed for site-specific delivery of active agents by selectively modifying the liposomal formulation.

In addition to the teachings of Couvreur *et al.* (1977; 1988), the following information may be utilized in generating liposomal formulations. Phospholipids can form a variety of structures other than liposomes when dispersed in water, depending on the molar ratio of lipid to water. At low ratios the liposome is the preferred structure. The physical characteristics of liposomes depend on pH, ionic strength and the presence of divalent cations. Liposomes can show low permeability to ionic and polar substances, but at elevated temperatures undergo a phase transition which markedly alters their permeability. The phase transition involves a change from a closely packed, ordered structure, known as the gel state, to a loosely packed, less-ordered structure, known as the fluid state. This occurs at a characteristic phase-transition temperature and results in an increase in permeability to ions, sugars and drugs.

In addition to temperature, exposure to proteins can alter the permeability of liposomes. Certain soluble proteins, such as cytochrome c, bind, deform and penetrate the bilayer, thereby causing changes in permeability. Cholesterol inhibits this penetration of proteins, apparently by packing the phospholipids more tightly. It is contemplated that the

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most useful liposome formations for antibiotic and inhibitor delivery will contain cholesterol.

The ability to trap solutes varies between different types of liposomes. For example, MLVs are moderately efficient at trapping solutes, but SUVs are extremely inefficient. SUVs offer the advantage of homogeneity and reproducibility in size distribution, however, and a compromise between size and trapping efficiency is offered by large unilamellar vesicles (LUVs). These are prepared by ether evaporation and are three to four times more efficient at solute entrapment than MLVs.

In addition to liposome characteristics, an important determinant in entrapping compounds is the physicochemical properties of the compound itself. Polar compounds are trapped in the aqueous spaces and nonpolar compounds bind to the lipid bilayer of the vesicle. Polar compounds are released through permeation or when the bilayer is broken, but nonpolar compounds remain affiliated with the bilayer unless it is disrupted by temperature or exposure to lipoproteins. Both types show maximum efflux rates at the phase transition temperature.

Liposomes interact with cells *via* four different mechanisms: endocytosis by phagocytic cells of the reticuloendothelial system such as macrophages and neutrophils; adsorption to the cell surface, either by nonspecific weak hydrophobic or electrostatic forces, or by specific interactions with cell-surface components; fusion with the plasma cell membrane by insertion of the lipid bilayer of the liposome into the plasma membrane, with simultaneous release of liposomal contents into the cytoplasm; and by transfer of liposomal lipids to cellular or subcellular membranes, or vice versa, without any association of the liposome contents. It often is difficult to determine which mechanism is operative and more than one may operate at the same time.

The fate and disposition of intravenously injected liposomes depend on their physical properties, such as size, fluidity, and surface charge. They may persist in tissues for h or days, depending on their composition, and half lives in the blood range from min to several h. Larger liposomes, such as MLVs and LUVs, are taken up rapidly by phagocytic cells of the reticuloendothelial system, but physiology of the circulatory system restrains

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the exit of such large species at most sites. They can exit only in places where large openings or pores exist in the capillary endothelium, such as the sinusoids of the liver or spleen. Thus, these organs are the predominate site of uptake. On the other hand, SUVs show a broader tissue distribution but still are sequestered highly in the liver and spleen. In general, this *in vivo* behavior limits the potential targeting of liposomes to only those organs and tissues accessible to their large size. These include the blood, liver, spleen, bone marrow, and lymphoid organs.

Targeting is generally not a limitation in terms of the present invention. However, should specific targeting be desired, methods are available for this to be accomplished. Antibodies may be used to bind to the liposome surface and to direct the antibody and its drug contents to specific antigenic receptors located on a particular cell-type surface. Carbohydrate determinants (glycoprotein or glycolipid cell-surface components that play a role in cell-cell recognition, interaction and adhesion) may also be used as recognition sites as they have potential in directing liposomes to particular cell types. Mostly, it is contemplated that intravenous injection of liposomal preparations would be used, but other routes of administration are also conceivable.

Alternatively, the invention provides for pharmaceutically-acceptable nanocapsule formulations of the compositions of the present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (Henry-Michelland *et al.*, 1987; Quintanar-Guerrero *et al.*, 1998; Douglas *et al.*, 1987). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1 µm) should be designed using polymers able to be degraded *in vivo*. Biodegradable polyalkyl-cyanoacrylate nanoparticles that meet these requirements are contemplated for use in the present invention. Such particles may be are easily made, as described (Couvreur *et al.*, 1980; 1988; zur Muhlen *et al.*, 1998; Zambaux *et al.* 1998; Pinto-Alphandry *et al.*, 1995 and U. S. Patent 5,145,684, specifically incorporated herein by reference in its entirety).

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#### **IMMUNOGENIC COMPOSITIONS**

In certain preferred embodiments of the present invention, immunogenic compositions, or vaccines, are provided. The immunogenic compositions will generally comprise one or more pharmaceutical compositions, such as those discussed above, in combination with an immunostimulant. An immunostimulant may be any substance that enhances or potentiates an immune response (antibody and/or cell-mediated) to an exogenous antigen. Examples of immunostimulants include adjuvants, biodegradable microspheres (e.g., polylactic galactide) and liposomes (into which the compound is incorporated; see e.g., Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and immunogenic compositions within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition.

Illustrative immunogenic compositions may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems* 15:143-198, 1998, and references cited therein. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for

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example, in Fisher-Hoch et al., Proc. Natl. Acad. Sci. USA 86:317-321, 1989; Flexner et al., Ann. N.Y. Acad. Sci. 569:86-103, 1989; Flexner et al., Vaccine 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, Biotechniques 6:616-627, 1988; Rosenfeld et al., Science 252:431-434, 1991; Kolls et al., Proc. Natl. Acad. Sci. USA 91:215-219, 1994; Kass-Eisler et al., Proc. Natl. Acad. Sci. USA 90:11498-11502, 1993; Guzman et al., Circulation 88:2838-2848, 1993; and Guzman et al., Cir. Res. 73:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., Science 259:1745-1749, 1993 and reviewed by Cohen, Science 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells. It will be apparent that an immunogenic composition may comprise both a polynucleotide and a polypeptide component. Such immunogenic compositions may provide for an enhanced immune response.

It will be apparent that an immunogenic composition may contain pharmaceutically acceptable salts of the polynucleotides and polypeptides provided herein. Such salts may be prepared from pharmaceutically acceptable non-toxic bases, including organic bases (e.g., salts of primary, secondary and tertiary amines and basic amino acids) and inorganic bases (e.g., sodium, potassium, lithium, ammonium, calcium and magnesium salts).

While any suitable carrier known to those of ordinary skill in the art may be employed in the compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate,

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sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (*e.g.*, polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763; 5,814,344 and 5,942,252. One may also employ a carrier comprising the particulate-protein complexes described in U.S. Patent No. 5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte responses in a host.

Such compositions may also comprise buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of immunostimulants may be employed in the immunogenic compositions of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bortadella pertussis* or *Mycobacterium tuberculosis* derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham, Philadelphia, PA); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

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Within the immunogenic compositions provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN-γ, TNFα, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of an immunogenic composition as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, Ann. Rev. Immunol. 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-Oacylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Corixa Corporation (Seattle, WA; see US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by Sato et al., Science 273:352, 1996. Another preferred adjuvant is a saponin, preferably QS21 (Aguila Biopharmaceuticals Inc., Framingham, MA), which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving OS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

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Other preferred adjuvants include Montanide ISA 720 (Seppic, France), SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series of adjuvants (e.g., SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the disclosures of which are incorporated herein by reference in their entireties.

Any immunogenic composition provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient. The compositions described herein may be administered as part of a sustained release formulation (*i.e.*, a formulation such as a capsule, sponge or gel (composed of polysaccharides, for example) that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology (*see*, *e.g.*, Coombes *et al.*, *Vaccine 14*:1429-1438, 1996) and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane.

Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. Such carriers include microparticles of poly(lactide-co-glycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other delayed-release carriers include supramolecular biovectors, which comprise a non-liquid hydrophilic core (e.g., a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer comprising an amphiphilic compound, such as a phospholipid (see e.g., U.S. Patent No. 5,151,254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

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Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and immunogenic compositions to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med. 50*:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within an immunogenic composition (*see Zitvogel et al.*, *Nature Med. 4:*594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4,

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IL-13 and/or TNF $\alpha$  to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNF $\alpha$ , CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcγ receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (e.g., CD54 and CD11) and costimulatory molecules (e.g., CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide encoding a prostate-specific protein (or portion or other variant thereof) such that the prostate-specific polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place *ex vivo*, and a composition comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi *et al.*, *Immunology and cell Biology 75*:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the prostate-specific polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (*e.g.*, vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently

conjugated to an immunological partner that provides T cell help (*e.g.*, a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

Immunogenic compositions and pharmaceutical compositions may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are preferably hermetically sealed to preserve sterility of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, a immunogenic composition or pharmaceutical composition may be stored in a freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

#### **CANCER THERAPY**

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In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as prostate cancer. Within such methods, pharmaceutical compositions and immunogenic compositions are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and immunogenic compositions may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and immunogenic compositions may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs. Administration may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host

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immune system to react against tumors with the administration of immune responsemodifying agents (such as polypeptides and polynucleotides as provided herein).

Within other embodiments. immunotherapy passive may immunotherapy, in which treatment involves the delivery of agents with established tumorimmune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8<sup>+</sup> cytotoxic T lymphocytes and CD4<sup>+</sup> T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*.

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Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al., Immunological Reviews 157:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and immunogenic compositions may be administered by injection (e.g., intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (i.e., untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells in vitro. Such immunogenic compositions should also be capable of causing an immune response that leads to an improved clinical outcome (e.g., more frequent remissions, complete or partial or longer disease-free survival) in treated patients as compared to non-treated patients. In general, for pharmaceutical compositions and immunogenic compositions comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

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In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (e.g., more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a prostate-specific protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

#### 10 CANCER DETECTION AND DIAGNOSIS

In general, a cancer may be detected in a patient based on the presence of one or more prostate-specific proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as prostate cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a prostate-specific sequence should be present at a level that is at least three fold higher in prostate tissue than in other normal tissues.

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length prostate-specific proteins and portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1

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hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about  $10 \text{ \mu g}$ , and preferably about 100 ng to about  $1 \text{ \mu g}$ , is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see*, *e.g.*, Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20<sup>™</sup> (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with prostate cancer. Preferably, the contact time is

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sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20<sup>™</sup>. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as prostate cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver

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Operator Curve, according to the method of Sackett et al., Clinical Epidemiology: A Basic Science for Clinical Medicine, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (i.e., sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (i.e., the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of

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antibody immobilized on the membrane ranges from about 25 ng to about 1µg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use prostate-specific polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such prostate-specific protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a prostate-specific protein in a biological sample. Within certain methods, a biological sample comprising CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient is incubated with a prostate-specific polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated in vitro for 2-9 days (typically 4 days) at 37°C with polypeptide (e.g., 5 - 25 μg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of prostatespecific polypeptide to serve as a control. For CD4<sup>+</sup> T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8<sup>+</sup> T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a prostate-specific protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction

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(PCR) based assay to amplify a portion of a prostate-specific cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the prostate-specific protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a prostate-specific protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a prostate-specific protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is

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not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the compositions described herein may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple prostate-specific protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

#### **DIAGNOSTIC KITS**

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for

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performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a prostate-specific protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a prostate-specific protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a prostate-specific protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a prostate-specific protein.

The following Examples are offered by way of illustration and not by way of limitation.

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#### EXAMPLE 1

## ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC POLYPEPTIDES

This Example describes the isolation of certain prostate-specific polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library was constructed from prostate tumor poly A<sup>+</sup> RNA using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD 20897) following the manufacturer's protocol. Specifically, prostate tumor tissues were homogenized with polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A<sup>+</sup> RNA was then purified using a Qiagen oligotex spin column mRNA purification kit (Qiagen, Santa Clarita, CA 91355) according to the manufacturer's protocol. First-strand cDNA was synthesized using the NotI/Oligo-dT18 primer. Double-stranded cDNA was synthesized, ligated with EcoRI/BAXI adaptors (Invitrogen, San Diego, CA) and digested with NotI. Following size fractionation with Chroma Spin-1000 columns (Clontech, Palo Alto, CA), the cDNA was ligated into the EcoRI/NotI site of pCDNA3.1 (Invitrogen) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure, a normal human pancreas cDNA expression library was prepared from a pool of six tissue specimens (Clontech). The cDNA libraries were characterized by determining the number of independent colonies, the percentage of clones that carried insert, the average insert size and by sequence analysis. The prostate tumor library contained  $1.64 \times 10^7$  independent colonies, with 70% of clones having an insert and the average insert size being 1745 base pairs. The normal pancreas cDNA library contained  $3.3 \times 10^6$  independent colonies, with 69% of clones having inserts and the average insert size being 1120 base pairs. For both libraries, sequence analysis showed that the majority of clones had a full length cDNA sequence and were synthesized from mRNA, with minimal rRNA and mitochondrial DNA contamination.

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cDNA library subtraction was performed using the above prostate tumor and normal pancreas cDNA libraries, as described by Hara *et al.* (*Blood*, *84*:189-199, 1994) with some modifications. Specifically, a prostate tumor-specific subtracted cDNA library was generated as follows. Normal pancreas cDNA library (70  $\mu$ g) was digested with EcoRI, NotI, and SfuI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 100  $\mu$ l of H<sub>2</sub>O, heat-denatured and mixed with 100  $\mu$ l (100  $\mu$ g) of Photoprobe biotin (Vector Laboratories, Burlingame, CA). As recommended by the manufacturer, the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional Photoprobe biotin (50  $\mu$ l) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23  $\mu$ l H<sub>2</sub>O to form the driver DNA.

To form the tracer DNA, 10 μg prostate tumor cDNA library was digested with BamHI and XhoI, phenol chloroform extracted and passed through Chroma spin-400 columns (Clontech). Following ethanol precipitation, the tracer DNA was dissolved in 5 μl H<sub>2</sub>O. Tracer DNA was mixed with 15 μl driver DNA and 20 μl of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 °C water bath and incubated for 20 hours (long hybridization [LH]). The reaction mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12 μl H<sub>2</sub>O, mixed with 8 μl driver DNA and 20 μl of 2 x hybridization buffer, and subjected to a hybridization at 68 °C for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted cDNA was ligated into BamHI/XhoI site of chloramphenicol resistant pBCSK<sup>+</sup> (Stratagene, La Jolla, CA 92037) and transformed into ElectroMax *E. coli* DH10B cells by electroporation to generate a prostate tumor specific subtracted cDNA library (referred to as "prostate subtraction 1").

To analyze the subtracted cDNA library, plasmid DNA was prepared from 100 independent clones, randomly picked from the subtracted prostate tumor specific

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library and grouped based on insert size. Representative cDNA clones were further characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A (Foster City, CA). Six cDNA clones, hereinafter referred to as F1-13, F1-12, F1-16, H1-1, H1-9 and H1-4, were shown to be abundant in the subtracted prostate-specific cDNA library. The determined 3' and 5' cDNA sequences for F1-12 are provided in SEQ ID NO: 2 and 3, respectively, with determined 3' cDNA sequences for F1-13, F1-16, H1-1, H1-9 and H1-4 being provided in SEQ ID NO: 1 and 4-7, respectively.

The cDNA sequences for the isolated clones were compared to known sequences in the gene bank using the EMBL and GenBank databases (release 96). Four of the prostate tumor cDNA clones, F1-13, F1-16, H1-1, and H1-4, were determined to encode the following previously identified proteins: prostate specific antigen (PSA), human glandular kallikrein, human tumor expression enhanced gene, and mitochondria cytochrome C oxidase subunit II. H1-9 was found to be identical to a previously identified human autonomously replicating sequence. No significant homologies to the cDNA sequence for F1-12 were found.

Subsequent studies led to the isolation of a full-length cDNA sequence for F1-12 (also referred to as P504S). This sequence is provided in SEQ ID NO: 107, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 108. cDNA splice variants of P504S are provided in SEQ ID NO: 600-605.

To clone less abundant prostate tumor specific genes, cDNA library subtraction was performed by subtracting the prostate tumor cDNA library described above with the normal pancreas cDNA library and with the three most abundant genes in the previously subtracted prostate tumor specific cDNA library: human glandular kallikrein, prostate specific antigen (PSA), and mitochondria cytochrome C oxidase subunit II. Specifically, 1 µg each of human glandular kallikrein, PSA and mitochondria cytochrome C oxidase subunit II cDNAs in pCDNA3.1 were added to the driver DNA and subtraction was performed as described above to provide a second subtracted cDNA library hereinafter referred to as the "subtracted prostate tumor specific cDNA library with spike".

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Twenty-two cDNA clones were isolated from the subtracted prostate tumor specific cDNA library with spike. The determined 3' and 5' cDNA sequences for the clones referred to as J1-17, L1-12, N1-1862, J1-13, J1-19, J1-25, J1-24, K1-58, K1-63, L1-4 and L1-14 are provided in SEQ ID NOS: 8-9, 10-11, 12-13, 14-15, 16-17, 18-19, 20-21, 22-23, 24-25, 26-27 and 28-29, respectively. The determined 3' cDNA sequences for the clones referred to as J1-12, J1-16, J1-21, K1-48, K1-55, L1-2, L1-6, N1-1858, N1-1860, N1-1861, N1-1864 are provided in SEQ ID NOS: 30-40, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to three of the five most abundant DNA species, (J1-17, L1-12 and N1-1862; SEQ ID NOS: 8-9, 10-11 and 12-13, respectively). Of the remaining two most abundant species, one (J1-12; SEQ ID NO:30) was found to be identical to the previously identified human pulmonary surfactant-associated protein, and the other (K1-48; SEQ ID NO:33) was determined to have some homology to R. norvegicus mRNA for 2-arylpropionyl-CoA epimerase. Of the 17 less abundant cDNA clones isolated from the subtracted prostate tumor specific cDNA library with spike, four (J1-16, K1-55, L1-6 and N1-1864; SEQ ID NOS:31, 34, 36 and 40, respectively) were found to be identical to previously identified sequences, two (J1-21 and N1-1860; SEQ ID NOS: 32 and 38, respectively) were found to show some homology to non-human sequences, and two (L1-2 and N1-1861; SEQ ID NOS: 35 and 39, respectively) were found to show some homology to known human sequences. No significant homologies were found to the polypeptides J1-13, J1-19, J1-24, J1-25, K1-58, K1-63, L1-4, L1-14 (SEQ ID NOS: 14-15, 16-17, 20-21, 18-19, 22-23, 24-25, 26-27, 28-29, respectively).

Subsequent studies led to the isolation of full length cDNA sequences for J1-17, L1-12 and N1-1862 (SEQ ID NOS: 109-111, respectively). The corresponding predicted amino acid sequences are provided in SEQ ID NOS: 112-114. L1-12 is also referred to as P501S. A cDNA splice variant of P501S is provided in SEQ ID NO: 606.

In a further experiment, four additional clones were identified by subtracting a prostate tumor cDNA library with normal prostate cDNA prepared from a pool of three normal prostate poly A+ RNA (referred to as "prostate subtraction 2"). The determined

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cDNA sequences for these clones, hereinafter referred to as U1-3064, U1-3065, V1-3692 and 1A-3905, are provided in SEQ ID NO: 69-72, respectively. Comparison of the determined sequences with those in the gene bank revealed no significant homologies to U1-3065.

A second subtraction with spike (referred to as "prostate subtraction spike 2") was performed by subtracting a prostate tumor specific cDNA library with spike with normal pancreas cDNA library and further spiked with PSA, J1-17, pulmonary surfactant-associated protein, mitochondrial DNA, cytochrome c oxidase subunit II, N1-1862, autonomously replicating sequence, L1-12 and tumor expression enhanced gene. Four additional clones, hereinafter referred to as V1-3686, R1-2330, 1B-3976 and V1-3679, were isolated. The determined cDNA sequences for these clones are provided in SEQ ID NO:73-76, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to V1-3686 and R1-2330.

Further analysis of the three prostate subtractions described above (prostate subtraction 2, subtracted prostate tumor specific cDNA library with spike, and prostate subtraction spike 2) resulted in the identification of sixteen additional clones, referred to as 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1G-4734, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4810, 1I-4811, 1J-4876, 1K-4884 and 1K-4896. The determined cDNA sequences for these clones are provided in SEQ ID NOS: 77-92, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to 1G-4741, 1G-4734, 1I-4807, 1J-4876 and 1K-4896 (SEQ ID NOS: 79, 81, 87, 90 and 92, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4807, 1J-4876, 1K-4884 and 1K-4896, provided in SEQ ID NOS: 179-188 and 191-193, respectively, and to the determination of additional partial cDNA sequences for 1I-4810 and 1I-4811, provided in SEQ ID NOS: 189 and 190, respectively.

Additional studies with prostate subtraction spike 2 resulted in the isolation of three more clones. Their sequences were determined as described above and compared

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to the most recent GenBank. All three clones were found to have homology to known genes, which are Cysteine-rich protein, KIAA0242, and KIAA0280 (SEQ ID NO: 317, 319, and 320, respectively). Further analysis of these clones by Synteni microarray (Synteni, Palo Alto, CA) demonstrated that all three clones were over-expressed in most prostate tumors and prostate BPH, as well as in the majority of normal prostate tissues tested, but low expression in all other normal tissues.

An additional subtraction was performed by subtracting a normal prostate cDNA library with normal pancreas cDNA (referred to as "prostate subtraction 3"). This led to the identification of six additional clones referred to as 1G-4761, 1G-4762, 1H-4766, 1H-4770, 1H-4771 and 1H-4772 (SEQ ID NOS: 93-98). Comparison of these sequences with those in the gene bank revealed no significant homologies to 1G-4761 and 1H-4771 (SEQ ID NOS: 93 and 97, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4761, 1G-4762, 1H-4766 and 1H-4772 provided in SEQ ID NOS: 194-196 and 199, respectively, and to the determination of additional partial cDNA sequences for 1H-4770 and 1H-4771, provided in SEQ ID NOS: 197 and 198, respectively.

Subtraction of a prostate tumor cDNA library, prepared from a pool of polyA+ RNA from three prostate cancer patients, with a normal pancreas cDNA library (prostate subtraction 4) led to the identification of eight clones, referred to as 1D-4297, 1D-4309, 1D.1-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280 (SEQ ID NOS: 99-107). These sequences were compared to those in the gene bank as described above. No significant homologies were found to 1D-4283 and 1D-4304 (SEQ ID NOS: 103 and 104, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1D-4309, 1D.1-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280, provided in SEQ ID NOS: 200-206, respectively.

cDNA clones isolated in prostate subtraction 1 and prostate subtraction 2, described above, were colony PCR amplified and their mRNA expression levels in prostate tumor, normal prostate and in various other normal tissues were determined using microarray technology (Synteni, Palo Alto, CA). Briefly, the PCR amplification products

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were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. This intensity correlates with the hybridization intensity. Two clones (referred to as P509S and P510S) were found to be over-expressed in prostate tumor and normal prostate and expressed at low levels in all other normal tissues tested (liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon). The determined cDNA sequences for P509S and P510S are provided in SEQ ID NO: 223 and 224, respectively. Comparison of these sequences with those in the gene bank as described above, revealed some homology to previously identified ESTs.

Additional, studies led to the isolation of the full-length cDNA sequence for P509S. This sequence is provided in SEQ ID NO: 332, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 339. Two variant full-length cDNA sequences for P510S are provided in SEQ ID NO: 535 and 536, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 537 and 538, respectively. Additional splice variants of P510S are provided in SEQ ID NO: 598 and 599.

The determined cDNA sequences for additional prostate-specific clones isolated during characterization of prostate specific cDNA libraries are provided in SEQ ID NO: 618-689, 691-697 and 709-772. Comparison of these sequences with those in the public databases revealed no significant homologies to any of these sequences.

## EXAMPLE 2

DETERMINATION OF TISSUE SPECIFICITY OF PROSTATE-SPECIFIC POLYPEPTIDES

Using gene specific primers, mRNA expression levels for the representative prostate-specific polypeptides F1-16, H1-1, J1-17 (also referred to as P502S), L1-12 (also

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referred to as P501S), F1-12 (also referred to as P504S) and N1-1862 (also referred to as P503S) were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent as described above. First strand synthesis was carried out using 1-2  $\mu g$  of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42  $^{0}$ C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR,  $\beta$ -actin was used as an internal control for each of the tissues examined. First, serial dilutions of the first strand cDNAs were prepared and RT-PCR assays were performed using  $\beta$ -actin specific primers. A dilution was then chosen that enabled the linear range amplification of the  $\beta$ -actin template and which was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the  $\beta$ -actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in four different types of tumor tissue (prostate tumor from 2 patients, breast tumor from 3 patients, colon tumor, lung tumor), and sixteen different normal tissues, including prostate, colon, kidney, liver, lung, ovary, pancreas, skeletal muscle, skin, stomach, testes, bone marrow and brain. F1-16 was found to be expressed at high levels in prostate tumor tissue, colon tumor and normal prostate, and at lower levels in normal liver, skin and testes, with expression being undetectable in the other tissues examined. H1-1 was found to be expressed at high levels in prostate tumor, lung tumor, breast tumor, normal prostate, normal colon and normal brain, at much lower levels in normal lung, pancreas, skeletal muscle, skin, small intestine, bone marrow, and was not detected in the other tissues tested. J1-17 (P502S) and L1-12 (P501S) appear to be specifically over-expressed in prostate, with both genes being expressed at high levels in prostate tumor and normal prostate but at low to undetectable levels in all the other tissues examined. N1-1862 (P503S) was found to be over-expressed in 60% of prostate tumors and detectable in normal colon and kidney. The RT-PCR results

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thus indicate that F1-16, H1-1, J1-17 (P502S), N1-1862 (P503S) and L1-12 (P501S) are either prostate specific or are expressed at significantly elevated levels in prostate.

Further RT-PCR studies showed that F1-12 (P504S) is over-expressed in 60% of prostate tumors, detectable in normal kidney but not detectable in all other tissues tested. Similarly, R1-2330 was shown to be over-expressed in 40% of prostate tumors, detectable in normal kidney and liver, but not detectable in all other tissues tested. U1-3064 was found to be over-expressed in 60% of prostate tumors, and also expressed in breast and colon tumors, but was not detectable in normal tissues.

RT-PCR characterization of R1-2330, U1-3064 and 1D-4279 showed that these three antigens are over-expressed in prostate and/or prostate tumors.

Northern analysis with four prostate tumors, two normal prostate samples, two BPH prostates, and normal colon, kidney, liver, lung, pancrease, skeletal muscle, brain, stomach, testes, small intestine and bone marrow, showed that L1-12 (P501S) is over-expressed in prostate tumors and normal prostate, while being undetectable in other normal tissues tested. J1-17 (P502S) was detected in two prostate tumors and not in the other tissues tested. N1-1862 (P503S) was found to be over-expressed in three prostate tumors and to be expressed in normal prostate, colon and kidney, but not in other tissues tested. F1-12 (P504S) was found to be highly expressed in two prostate tumors and to be undetectable in all other tissues tested.

The microarray technology described above was used to determine the expression levels of representative antigens described herein in prostate tumor, breast tumor and the following normal tissues: prostate, liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon. L1-12 (P501S) was found to be over-expressed in normal prostate and prostate tumor, with some expression being detected in normal skeletal muscle. Both J1-12 and F1-12 (P504S) were found to be over-expressed in prostate tumor, with expression being lower or undetectable in all other tissues tested. N1-1862 (P503S) was found to be expressed at high levels in prostate tumor and normal prostate, and at low levels in normal large intestine and normal colon, with expression

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being undetectable in all other tissues tested. R1-2330 was found to be over-expressed in prostate tumor and normal prostate, and to be expressed at lower levels in all other tissues tested. 1D-4279 was found to be over-expressed in prostate tumor and normal prostate, expressed at lower levels in normal spinal cord, and to be undetectable in all other tissues tested.

Further microarray analysis to specifically address the extent to which P501S (SEQ ID NO: 110) was expressed in breast tumor revealed moderate over-expression not only in breast tumor, but also in metastatic breast tumor (2/31), with negligible to low expression in normal tissues. This data suggests that P501S may be over-expressed in various breast tumors as well as in prostate tumors.

The expression levels of 32 ESTs (expressed sequence tags) described by Vasmatzis *et al.* (*Proc. Natl. Acad. Sci. USA 95*:300-304, 1998) in a variety of tumor and normal tissues were examined by microarray technology as described above. Two of these clones (referred to as P1000C and P1001C) were found to be over-expressed in prostate tumor and normal prostate, and expressed at low to undetectable levels in all other tissues tested (normal aorta, thymus, resting and activated PBMC, epithelial cells, spinal cord, adrenal gland, fetal tissues, skin, salivary gland, large intestine, bone marrow, liver, lung, dendritic cells, stomach, lymph nodes, brain, heart, small intestine, skeletal muscle, colon and kidney. The determined cDNA sequences for P1000C and P1001C are provided in SEQ ID NO: 384 and 472, respectively. The sequence of P1001C was found to show some homology to the previously isolated Human mRNA for JM27 protein. No significant homologies were found to the sequence of P1000C.

The expression of the polypeptide encoded by the full length cDNA sequence for F1-12 (also referred to as P504S; SEQ ID NO: 108) was investigated by immunohistochemical analysis. Rabbit-anti-P504S polyclonal antibodies were generated against the full length P504S protein by standard techniques. Subsequent isolation and characterization of the polyclonal antibodies were also performed by techniques well known in the art. Immunohistochemical analysis showed that the P504S polypeptide was expressed in 100% of prostate carcinoma samples tested (n=5).

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The rabbit-anti-P504S polyclonal antibody did not appear to label benign prostate cells with the same cytoplasmic granular staining, but rather with light nuclear staining. Analysis of normal tissues revealed that the encoded polypeptide was found to be expressed in some, but not all normal human tissues. Positive cytoplasmic staining with rabbit-anti-P504S polyclonal antibody was found in normal human kidney, liver, brain, colon and lung-associated macrophages, whereas heart and bone marrow were negative.

This data indicates that the P504S polypeptide is present in prostate cancer tissues, and that there are qualitative and quantitative differences in the staining between benign prostatic hyperplasia tissues and prostate cancer tissues, suggesting that this polypeptide may be detected selectively in prostate tumors and therefore be useful in the diagnosis of prostate cancer.

## EXAMPLE 3

## ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC POLYPEPTIDES BY PCR-BASED SUBTRACTION

A cDNA subtraction library, containing cDNA from normal prostate subtracted with ten other normal tissue cDNAs (brain, heart, kidney, liver, lung, ovary, placenta, skeletal muscle, spleen and thymus) and then submitted to a first round of PCR amplification, was purchased from Clontech. This library was subjected to a second round of PCR amplification, following the manufacturer's protocol. The resulting cDNA fragments were subcloned into the vector pT7 Blue T-vector (Novagen, Madison, WI) and transformed into XL-1 Blue MRF' *E. coli* (Stratagene). DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A.

Fifty-nine positive clones were sequenced. Comparison of the DNA sequences of these clones with those in the gene bank, as described above, revealed no significant homologies to 25 of these clones, hereinafter referred to as P5, P8, P9, P18, P20, P30, P34, P36, P38, P39, P42, P49, P50, P53, P55, P60, P64, P65, P73, P75, P76, P79

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and P84. The determined cDNA sequences for these clones are provided in SEQ ID NO: 41-45, 47-52 and 54-65, respectively. P29, P47, P68, P80 and P82 (SEQ ID NO: 46, 53 and 66-68, respectively) were found to show some degree of homology to previously identified DNA sequences. To the best of the inventors' knowledge, none of these sequences have been previously shown to be present in prostate.

Further studies employing the sequence of SEQ ID NO: 67 as a probe in standard full-length cloning methods, resulted in the isolation of three cDNA sequences which appear to be splice variants of P80 (also known as P704P). These sequences are provided in SEQ ID NO: 699-701.

Further studies using the PCR-based methodology described above resulted in the isolation of more than 180 additional clones, of which 23 clones were found to show no significant homologies to known sequences. The determined cDNA sequences for these clones are provided in SEQ ID NO: 115-123, 127, 131, 137, 145, 147-151, 153, 156-158 and 160. Twenty-three clones (SEQ ID NO: 124-126, 128-130, 132-136, 138-144, 146, 152, 154, 155 and 159) were found to show some homology to previously identified ESTs. An additional ten clones (SEQ ID NO: 161-170) were found to have some degree of homology to known genes. Larger cDNA clones containing the P20 sequence represent splice variants of a gene referred to as P703P. The determined DNA sequence for the variants referred to as DE1, DE13 and DE14 are provided in SEQ ID NOS: 171, 175 and 177, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 172, 176 and 178, respectively. The determined cDNA sequence for an extended spliced form of P703 is provided in SEQ ID NO: 225. The DNA sequences for the splice variants referred to as DE2 and DE6 are provided in SEQ ID NOS: 173 and 174, respectively.

mRNA Expression levels for representative clones in tumor tissues (prostate (n=5), breast (n=2), colon and lung) normal tissues (prostate (n=5), colon, kidney, liver, lung (n=2), ovary (n=2), skeletal muscle, skin, stomach, small intestine and brain), and activated and non-activated PBMC was determined by RT-PCR as described above. Expression was examined in one sample of each tissue type unless otherwise indicated.

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P9 was found to be highly expressed in normal prostate and prostate tumor compared to all normal tissues tested except for normal colon which showed comparable expression. P20, a portion of the P703P gene, was found to be highly expressed in normal prostate and prostate tumor, compared to all twelve normal tissues tested. A modest increase in expression of P20 in breast tumor (n=2), colon tumor and lung tumor was seen compared to all normal tissues except lung (1 of 2). Increased expression of P18 was found in normal prostate, prostate tumor and breast tumor compared to other normal tissues except lung and stomach. A modest increase in expression of P5 was observed in normal prostate compared to most other normal tissues. However, some elevated expression was seen in normal lung and PBMC. Elevated expression of P5 was also observed in prostate tumors (2 of 5), breast tumor and one lung tumor sample. For P30, similar expression levels were seen in normal prostate and prostate tumor, compared to six of twelve other normal tissues tested. Increased expression was seen in breast tumors, one lung tumor sample and one colon tumor sample, and also in normal PBMC. P29 was found to be overexpressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to the majority of normal tissues. However, substantial expression of P29 was observed in normal colon and normal lung (2 of 2). P80 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to all other normal tissues tested, with increased expression also being seen in colon tumor.

Further studies resulted in the isolation of twelve additional clones, hereinafter referred to as 10-d8, 10-h10, 11-c8, 7-g6, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3, 8-h11, 9-f12 and 9-f3. The determined DNA sequences for 10-d8, 10-h10, 11-c8, 8-d4, 8-d9, 8-h11, 9-f12 and 9-f3 are provided in SEQ ID NO: 207, 208, 209, 216, 217, 220, 221 and 222, respectively. The determined forward and reverse DNA sequences for 7-g6, 8-b5, 8-b6 and 8-g3 are provided in SEQ ID NO: 210 and 211; 212 and 213; 214 and 215; and 218 and 219, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to the sequence of 9-f3. The clones 10-d8, 11-c8 and 8-h11 were found to show some homology to previously isolated ESTs, while 10-h10, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3 and 9-f12 were found to show some homology to previously identified genes.

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Further characterization of 7-G6 and 8-G3 showed identity to the known genes PAP and PSA, respectively.

mRNA expression levels for these clones were determined using the micro-array technology described above. The clones 7-G6, 8-G3, 8-B5, 8-B6, 8-D4, 8-D9, 9-F3, 9-F12, 9-H3, 10-A2, 10-A4, 11-C9 and 11-F2 were found to be over-expressed in prostate tumor and normal prostate, with expression in other tissues tested being low or undetectable. Increased expression of 8-F11 was seen in prostate tumor and normal prostate, bladder, skeletal muscle and colon. Increased expression of 10-H10 was seen in prostate tumor and normal prostate, bladder, lung, colon, brain and large intestine. Increased expression of 9-B1 was seen in prostate tumor, breast tumor, and normal prostate, salivary gland, large intestine and skin, with increased expression of 11-C8 being seen in prostate tumor, and normal prostate and large intestine.

An additional cDNA fragment derived from the PCR-based normal prostate subtraction, described above, was found to be prostate specific by both micro-array technology and RT-PCR. The determined cDNA sequence of this clone (referred to as 9-A11) is provided in SEQ ID NO: 226. Comparison of this sequence with those in the public databases revealed 99% identity to the known gene HOXB13.

Further studies led to the isolation of the clones 8-C6 and 8-H7. The determined cDNA sequences for these clones are provided in SEQ ID NO: 227 and 228, respectively. These sequences were found to show some homology to previously isolated ESTs.

PCR and hybridization-based methodologies were employed to obtain longer cDNA sequences for clone P20 (also referred to as P703P), yielding three additional cDNA fragments that progressively extend the 5' end of the gene. These fragments, referred to as P703PDE5, P703P6.26, and P703PX-23 (SEQ ID NO: 326, 328 and 330, with the predicted corresponding amino acid sequences being provided in SEQ ID NO: 327, 329 and 331, respectively) contain additional 5' sequence. P703PDE5 was recovered by screening of a cDNA library (#141-26) with a portion of P703P as a probe. P703P6.26 was recovered from a mixture of three prostate tumor cDNAs and P703PX 23 was

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recovered from cDNA library (#438-48). Together, the additional sequences include all of the putative mature serine protease along with part of the putative signal sequence. The full-length cDNA sequence for P703P is provided in SEQ ID NO: 524, with the corresponding amino acid sequence being provided in SEQ ID NO: 525.

P703P was found to show some homology to previously identified proteases, such as thrombin. The thrombin receptor has been shown to be preferentially expressed in highly metastatic breast carcinoma cells and breast carcinoma biopsy samples. Introduction of thrombin receptor antisense cDNA has been shown to inhibit the invasion of metastatic breast carcinoma cells in culture. Antibodies against thrombin receptor inhibit thrombin receptor activation and thrombin-induced platelet activation. Furthermore, peptides that resemble the receptor's tethered ligand domain inhibit platelet aggregation by thrombin. P703P may play a role in prostate cancer through a proteaseactivated receptor on the cancer cell or on stromal cells. The potential trypsin-like protease activity of P703P may either activate a protease-activated receptor on the cancer cell membrane to promote tumorgenesis or activate a protease-activated receptor on the adjacent cells (such as stromal cells) to secrete growth factors and/or proteases (such as matrix metalloproteinases) that could promote tumor angiogenesis, invasion and metastasis. P703P may thus promote tumor progression and/or metastasis through the activation of protease-activated receptor. Polypeptides and antibodies that block the P703P-receptor interaction may therefore be usefully employed in the treatment of prostate cancer.

Further studies using a PCR-based subtraction library of a prostate tumor pool subtracted against a pool of normal tissues (referred to as JP: PCR subtraction) resulted in the isolation of thirteen additional clones, seven of which did not share any significant homology to known GenBank sequences. The determined cDNA sequences for these seven clones (P711P, P712P, novel 23, P774P, P775P, P710P and P768P) are provided in SEQ ID NO: 307-311, 313 and 315, respectively. The remaining six clones (SEQ ID NO: 316 and 321-325) were shown to share some homology to known genes. By microarray analysis, all thirteen clones showed three or more fold over-expression in

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prostate tissues, including prostate tumors, BPH and normal prostate as compared to normal non-prostate tissues. Clones P711P, P712P, novel 23 and P768P showed over-expression in most prostate tumors and BPH tissues tested (n=29), and in the majority of normal prostate tissues (n=4), but background to low expression levels in all normal tissues. Clones P774P, P775P and P710P showed comparatively lower expression and expression in fewer prostate tumors and BPH samples, with negative to low expression in normal prostate.

Further studies led to the isolation of an extended cDNA sequence for P712P (SEQ ID NO: 552). The amino acid sequences encoded by 16 predicted open reading frames present within the sequence of SEQ ID NO: 552 are provided in SEQ ID NO: 553-568.

The full-length cDNA for P711P was obtained by employing the partial sequence of SEQ ID NO: 307 to screen a prostate cDNA library. Specifically, a directionally cloned prostate cDNA library was prepared using standard techniques. One million colonies of this library were plated onto LB/Amp plates. Nylon membrane filters were used to lift these colonies, and the cDNAs which were picked up by these filters were denatured and cross-linked to the filters by UV light. The P711P cDNA fragment of SEQ ID NO: 307 was radio-labeled and used to hybridize with these filters. Positive clones were selected, and cDNAs were prepared and sequenced using an automatic Perkin Elmer/Applied Biosystems sequencer. The determined full-length sequence of P711P is provided in SEQ ID NO: 382, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 383.

Using PCR and hybridization-based methodologies, additional cDNA sequence information was derived for two clones described above, 11-C9 and 9-F3, herein after referred to as P707P and P714P, respectively (SEQ ID NO: 333 and 334). After comparison with the most recent GenBank, P707P was found to be a splice variant of the known gene HoxB13. In contrast, no significant homologies to P714P were found. Further studies employing the sequence of SEQ ID NO: 334 as a probe in standard full-length cloning methods, resulted in an extended cDNA sequence for P714P. This sequence

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is provided in SEQ ID NO: 698. This sequence was found to show some homology to the gene that encodes human ribosomal L23A protein.

Clones 8-B3, P89, P98, P130 and P201 (as disclosed in U.S. Patent Application No. 09/020,956, filed February 9, 1998) were found to be contained within one contiguous sequence, referred to as P705P (SEQ ID NO: 335, with the predicted amino acid sequence provided in SEQ ID NO: 336), which was determined to be a splice variant of the known gene NKX 3.1.

Further studies on P775P resulted in the isolation of four additional sequences (SEQ ID NO: 473-476) which are all splice variants of the P775P gene. The sequence of SEQ ID NO: 474 was found to contain two open reading frames (ORFs). The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 477 and 478. The cDNA sequence of SEQ ID NO: 475 was found to contain an ORF which encodes the amino acid sequence of SEQ ID NO: 479. The cDNA sequence of SEQ ID NO: 473 was found to contain four ORFs. The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 480-483. Additional splice variants of P775P are provided in SEQ ID NO: 593-597.

Subsequent studies led to the identification of a genomic region on chromosome 22q11.2, known as the Cat Eye Syndrome region, that contains the five prostate genes P704P, P712P, P774P, P775P and B305D. The relative location of each of these five genes within the genomic region is shown in Fig. 10. This region may therefore be associated with malignant tumors, and other potential tumor genes may be contained within this region. These studies also led to the identification of a potential open reading frame (ORF) for P775P (provided in SEQ ID NO: 533), which encodes the amino acid sequence of SEQ ID NO: 534.

Comparison of the clone of SEQ ID NO: 325 (referred to as P558S) with sequences in the GenBank and GeneSeq DNA databases showed that P558S is identical to the prostate-specific transglutaminase gene, which is known to have two forms. The full-length sequences for the two forms are provided in SEQ ID NO: 773 and 774, with the corresponding amino acid sequences being provided in SEQ ID NO: 775 and 776,

respectively. The cDNA sequence of SEQ ID NO: 774 has a 15 pair base insert, resulting in a 5 amino acid insert in the corresponding amino acid sequence (SEQ ID NO: 776). This insert is not present in the sequence of SEQ ID NO: 773.

EXAMPLE 4

### SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

## **EXAMPLE 5**

# FURTHER ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC POLYPEPTIDES BY PCR-BASED SUBTRACTION

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A cDNA library generated from prostate primary tumor mRNA as described above was subtracted with cDNA from normal prostate. The subtraction was performed using a PCR-based protocol (Clontech), which was modified to generate larger fragments. Within this protocol, tester and driver double stranded cDNA were separately digested with

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five restriction enzymes that recognize six-nucleotide restriction sites (MluI, MscI, PvuII, SalI and StuI). This digestion resulted in an average cDNA size of 600 bp, rather than the average size of 300 bp that results from digestion with RsaI according to the Clontech protocol. This modification did not affect the subtraction efficiency. Two tester populations were then created with different adapters, and the driver library remained without adapters.

The tester and driver libraries were then hybridized using excess driver cDNA. In the first hybridization step, driver was separately hybridized with each of the two tester cDNA populations. This resulted in populations of (a) unhybridized tester cDNAs, (b) tester cDNAs hybridized to other tester cDNAs, (c) tester cDNAs hybridized to driver cDNAs and (d) unhybridized driver cDNAs. The two separate hybridization reactions were then combined, and rehybridized in the presence of additional denatured driver cDNA. Following this second hybridization, in addition to populations (a) through (d), a fifth population (e) was generated in which tester cDNA with one adapter hybridized to tester cDNA with the second adapter. Accordingly, the second hybridization step resulted in enrichment of differentially expressed sequences which could be used as templates for PCR amplification with adaptor-specific primers.

The ends were then filled in, and PCR amplification was performed using adaptor-specific primers. Only population (e), which contained tester cDNA that did not hybridize to driver cDNA, was amplified exponentially. A second PCR amplification step was then performed, to reduce background and further enrich differentially expressed sequences.

This PCR-based subtraction technique normalizes differentially expressed cDNAs so that rare transcripts that are overexpressed in prostate tumor tissue may be recoverable. Such transcripts would be difficult to recover by traditional subtraction methods.

In addition to genes known to be overexpressed in prostate tumor, seventy-seven further clones were identified. Sequences of these partial cDNAs are provided in SEQ ID NO: 29 to 305. Most of these clones had no significant homology to database

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sequences. Exceptions were JPTPN23 (SEQ ID NO: 231; similarity to pig valosin-containing protein), JPTPN30 (SEQ ID NO: 234; similarity to rat mRNA for proteasome subunit), JPTPN45 (SEQ ID NO: 243; similarity to rat *norvegicus* cytosolic NADP-dependent isocitrate dehydrogenase), JPTPN46 (SEQ ID NO: 244; similarity to human subclone H8 4 d4 DNA sequence), JP1D6 (SEQ ID NO: 265; similarity to *G. gallus* dynein light chain-A), JP8D6 (SEQ ID NO: 288; similarity to human BAC clone RG016J04), JP8F5 (SEQ ID NO: 289; similarity to human subclone H8 3 b5 DNA sequence), and JP8E9 (SEQ ID NO: 299; similarity to human Alu sequence).

Additional studies using the PCR-based subtraction library consisting of a prostate tumor pool subtracted against a normal prostate pool (referred to as PT-PN PCR subtraction) yielded three additional clones. Comparison of the cDNA sequences of these clones with the most recent release of GenBank revealed no significant homologies to the two clones referred to as P715P and P767P (SEQ ID NO: 312 and 314). The remaining clone was found to show some homology to the known gene KIAA0056 (SEQ ID NO: 318). Using microarray analysis to measure mRNA expression levels in various tissues, all three clones were found to be over-expressed in prostate tumors and BPH tissues. Specifically, clone P715P was over-expressed in most prostate tumors and BPH tissues by a factor of three or greater, with elevated expression seen in the majority of normal prostate samples and in fetal tissue, but negative to low expression in all other normal tissues. Clone P767P was over-expressed in several prostate tumors and BPH tissues, with moderate expression levels in half of the normal prostate samples, and background to low expression in all other normal tissues tested.

Further analysis, by microarray as described above, of the PT-PN PCR subtraction library and of a DNA subtraction library containing cDNA from prostate tumor subtracted with a pool of normal tissue cDNAs, led to the isolation of 27 additional clones (SEQ ID NO: 340-365 and 381) which were determined to be over-expressed in prostate tumor. The clones of SEQ ID NO: 341, 342, 345, 347, 348, 349, 351, 355-359, 361, 362 and 364 were also found to be expressed in normal prostate. Expression of all 26 clones in a variety of normal tissues was found to be low or undetectable, with the exception of

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P544S (SEQ ID NO: 356) which was found to be expressed in small intestine. Of the 26 clones, 11 (SEQ ID NO: 340-349 and 362) were found to show some homology to previously identified sequences. No significant homologies were found to the clones of SEQ ID NO: 350, 351, 353-361, and 363-365.

Comparison of the sequence of SEQ ID NO: 362 with sequences in the GenBank and GeneSeq DNA databases showed that this clone (referred to as P788P) is identical to GeneSeq Accession No. X27262, which encodes a protein found in the GeneSeq protein Accession No. Y00931. The full length cDNA sequence of P788P is shown in Figure 12A (SEQ ID NO: 777), with the corresponding predicted amino acid being shown in Figure 12B (SEQ ID NO: 778). Subsequently, a full-length cDNA sequence for P788P that contains polymorphisms not found in the sequence of SEQ ID NO: 779, was cloned multiple times by PCR amplification from cDNA prepared from several RNA templates from three individuals. This determined cDNA sequence of this polymorphic variant of P788P is provided in SEQ ID NO: 779, with the corresponding amino acid sequence being provided in SEQ ID NO: 780. The sequence of SEQ ID NO: 780 differs from that of SEQ ID NO: 778 by six amino acid residues.

Further studies on the clone of SEQ ID NO: 352 (referred to as P790P) led to the isolation of the full-length cDNA sequence of SEQ ID NO: 526. The corresponding predicted amino acid is provided in SEQ ID NO: 527. Data from two quantitative PCR experiments indicated that P790P is over-expressed in 11/15 tested prostate tumor samples and is expressed at low levels in spinal cord, with no expression being seen in all other normal samples tested. Data from further PCR experiments and microarray experiments showed over-expression in normal prostate and prostate tumor with little or no expression in other tissues tested. P790P was subsequently found to show significant homology to a previously identified G-protein coupled prostate tissue receptor.

Additional studies on the clone of SEQ ID NO: 354 (referred to as P776P) led to the isolation of an extended cDNA sequence, provided in SEQ ID NO: 569. The determined cDNA sequences of three additional splice variants of P776P are provided in SEQ ID NO: 570-572. The amino acid sequences encoded by two predicted open reading

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frames (ORFs) contained within SEQ ID NO: 570, one predicted ORF contained within SEO ID NO: 571, and 11 predicted ORFs contained within SEQ ID NO: 569, are provided in SEO ID NO: 573-586, respectively.

Comparison of the cDNA sequences for the clones P767P (SEQ ID NO: 314) and P777P (SEO ID NO: 350) with sequences in the GenBank human EST database showed that the two clones matched many EST sequences in common, suggesting that P767P and P777P may represent the same gene. A DNA consensus sequence derived from a DNA sequence alignment of P767P, P777P and multiple EST clones is provided in SEQ ID NO: 587. The amino acid sequences encoded by three putative ORFs located within SEO ID NO: 587 are provided in SEQ ID NO: 588-590. 10

### **EXAMPLE 6**

### PEPTIDE PRIMING OF MICE AND PROPAGATION OF CTL LINES

6.1. This Example illustrates the preparation of a CTL cell line specific for cells expressing the P502S gene.

Mice expressing the transgene for human HLA A2Kb (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with P2S#12 peptide (VLGWVAEL; SEQ ID NO: 306), which is derived from the P502S gene (also referred to herein as J1-17, SEQ ID NO: 8), as described by Theobald et al., Proc. Natl. Acad. Sci. USA 92:11993-11997, 1995 with the following modifications. Mice were immunized with 100µg of P2S#12 and 120µg of an I-A<sup>b</sup> binding peptide derived from hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and using a nylon mesh single cell suspensions prepared. Cells were then resuspended at 6 x 10<sup>6</sup> cells/ml in complete media (RPMI-1640; Gibco BRL, Gaithersburg, MD) containing 10% FCS, 2mM Glutamine (Gibco BRL), sodium pyruvate (Gibco BRL), non-essential amino acids (Gibco BRL), 2 x 10<sup>-5</sup> M 2-mercaptoethanol, 50U/ml penicillin and streptomycin, and cultured in the presence of irradiated (3000 rads) P2S#12-pulsed (5mg/ml P2S#12 and 10mg/ml β2-microglobulin) LPS blasts (A2

transgenic spleens cells cultured in the presence of  $7\mu g/ml$  dextran sulfate and  $25\mu g/ml$  LPS for 3 days). Six days later, cells (5 x  $10^5/ml$ ) were restimulated with 2.5 x  $10^6/ml$  peptide pulsed irradiated (20,000 rads) EL4A2Kb cells (Sherman et al, *Science 258*:815-818, 1992) and 3 x  $10^6/ml$  A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20U/ml IL-2. Cells continued to be restimulated on a weekly basis as described, in preparation for cloning the line.

P2S#12 line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells ( $1 \times 10^4$  cells/ well) as stimulators and A2 transgenic spleen cells as feeders ( $5 \times 10^5$  cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, clones that were growing were isolated and maintained in culture. Several of these clones demonstrated significantly higher reactivity (lysis) against human fibroblasts (HLA A2Kb expressing) transduced with P502S than against control fibroblasts. An example is presented in Figure 1.

This data indicates that P2S #12 represents a naturally processed epitope of the P502S protein that is expressed in the context of the human HLA A2Kb molecule.

6.2. This Example illustrates the preparation of murine CTL lines and CTL clones specific for cells expressing the P501S gene.

This series of experiments were performed similarly to that described above.

Mice were immunized with the P1S#10 peptide (SEQ ID NO: 337), which is derived from the P501S gene (also referred to herein as L1-12, SEQ ID NO: 110). The P1S#10 peptide was derived by analysis of the predicted polypeptide sequence for P501S for potential HLA-A2 binding sequences as defined by published HLA-A2 binding motifs (Parker, KC, et al, J. Immunol., 152:163, 1994). P1S#10 peptide was synthesized as described in Example 4, and empirically tested for HLA-A2 binding using a T cell based competition assay. Predicted A2 binding peptides were tested for their ability to compete HLA-A2 specific peptide presentation to an HLA-A2 restricted CTL clone (D150M58), which is specific for the HLA-A2 binding influenza matrix peptide fluM58. D150M58 CTL secretes TNF in response to self-presentation of peptide fluM58. In the competition assay,

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test peptides at 100-200 µg/ml were added to cultures of D150M58 CTL in order to bind HLA-A2 on the CTL. After thirty minutes, CTL cultured with test peptides, or control peptides, were tested for their antigen dose response to the fluM58 peptide in a standard TNF bioassay. As shown in Figure 3, peptide P1S#10 competes HLA-A2 restricted presentation of fluM58, demonstrating that peptide P1S#10 binds HLA-A2.

Mice expressing the transgene for human HLA A2Kb were immunized as described by Theobald et al. (Proc. Natl. Acad. Sci. USA 92:11993-11997, 1995) with the following modifications. Mice were immunized with 62.5µg of P1S #10 and 120µg of an I-A<sup>b</sup> binding peptide derived from Hepatitis B Virus protein emulsified in incomplete Three weeks later these mice were sacrificed and single cell Freund's adjuvant. suspensions prepared using a nylon mesh. Cells were then resuspended at 6 x 10<sup>6</sup> cells/ml in complete media (as described above) and cultured in the presence of irradiated (3000 rads) P1S#10-pulsed (2μg/ml P1S#10 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7µg/ml dextran sulfate and 25µg/ml LPS for 3 days). Six days later cells (5 x  $10^5$ /ml) were restimulated with 2.5 x  $10^6$ /ml peptide-pulsed irradiated (20,000 rads) EL4A2Kb cells, as described above, and 3 x  $10^6$ /ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20 U/ml IL-2. Cells were restimulated on a weekly basis in preparation for cloning. After three rounds of in vitro stimulations, one line was generated that recognized P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat targets as shown in Figure 4.

A P1S#10-specific CTL line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells (1 x 10<sup>4</sup> cells/ well) as stimulators and A2 transgenic spleen cells as feeders (5 x 10<sup>5</sup> cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, viable clones were isolated and maintained in culture. As shown in Figure 5, five of these clones demonstrated specific cytolytic reactivity against P501S-transduced Jurkat A2Kb targets. This data indicates that P1S#10 represents a naturally processed epitope of the P501S protein that is expressed in the context of the human HLA-A2.1 molecule.

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### EXAMPLE 7

### PRIMING OF CTL IN VIVO USING NAKED DNA IMMUNIZATION

#### WITH A PROSTATE ANTIGEN

The prostate-specific antigen L1-12, as described above, is also referred to as P501S. HLA A2Kb Tg mice (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with 100 µg P501S in the vector VR1012 either intramuscularly or intradermally. The mice were immunized three times, with a two week interval between immunizations. Two weeks after the last immunization, immune spleen cells were cultured with Jurkat A2Kb-P501S transduced stimulator cells. CTL lines were stimulated weekly. After two weeks of *in vitro* stimulation, CTL activity was assessed against P501S transduced targets. Two out of 8 mice developed strong anti-P501S CTL responses. These results demonstrate that P501S contains at least one naturally processed HLA-A2-restricted CTL epitope.

15 EXAMPLE 8

ABILITY OF HUMAN T CELLS TO RECOGNIZE PROSTATE-SPECIFIC POLYPEPTIDES

This Example illustrates the ability of T cells specific for a prostate tumor polypeptide to recognize human tumor.

Human CD8<sup>+</sup> T cells were primed *in vitro* to the P2S-12 peptide (SEQ ID NO: 306) derived from P502S (also referred to as J1-17) using dendritic cells according to the protocol of Van Tsai et al. (*Critical Reviews in Immunology 18*:65-75, 1998). The resulting CD8<sup>+</sup> T cell microcultures were tested for their ability to recognize the P2S-12 peptide presented by autologous fibroblasts or fibroblasts which were transduced to express the P502S gene in a  $\gamma$ -interferon ELISPOT assay (*see* Lalvani et al., *J. Exp. Med. 186*:859-865, 1997). Briefly, titrating numbers of T cells were assayed in duplicate on  $10^4$  fibroblasts in the presence of 3  $\mu$ g/ml human  $\beta$ 2-microglobulin and 1  $\mu$ g/ml P2S-12 peptide or control E75 peptide. In addition, T cells were simultaneously assayed on autologous fibroblasts transduced with the P502S gene or as a control, fibroblasts transduced with

HER-2/neu. Prior to the assay, the fibroblasts were treated with 10 ng/ml γ-interferon for 48 hours to upregulate class I MHC expression. One of the microcultures (#5) demonstrated strong recognition of both peptide pulsed fibroblasts as well as transduced fibroblasts in a γ-interferon ELISPOT assay. Figure 2A demonstrates that there was a strong increase in the number of γ-interferon spots with increasing numbers of T cells on fibroblasts pulsed with the P2S-12 peptide (solid bars) but not with the control E75 peptide (open bars). This shows the ability of these T cells to specifically recognize the P2S-12 peptide. As shown in Figure 2B, this microculture also demonstrated an increase in the number of γ-interferon spots with increasing numbers of T cells on fibroblasts transduced to express the P502S gene but not the HER-2/neu gene. These results provide additional confirmatory evidence that the P2S-12 peptide is a naturally processed epitope of the P502S protein. Furthermore, this also demonstrates that there exists in the human T cell repertoire, high affinity T cells which are capable of recognizing this epitope. These T cells should also be capable of recognizing human tumors which express the P502S gene.

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### **EXAMPLE 9**

## ELICITATION OF PROSTATE ANTIGEN-SPECIFIC CTL RESPONSES IN HUMAN BLOOD

This Example illustrates the ability of a prostate-specific antigen to elicit a CTL response in blood of normal humans.

Autologous dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal donors by growth for five days in RPMI medium containing 10% human serum, 50 ng/ml GMCSF and 30 ng/ml IL-4. Following culture, DC were infected overnight with recombinant P501S-expressing vaccinia virus at an M.O.I. of 5 and matured for 8 hours by the addition of 2 micrograms/ml CD40 ligand. Virus was inactivated by UV irradiation, CD8<sup>+</sup> cells were isolated by positive selection using magnetic beads, and priming cultures were initiated in 24-well plates. Following five stimulation cycles using autologous fibroblasts retrovirally transduced to express P501S

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and CD80, CD8+ lines were identified that specifically produced interferon-gamma when stimulated with autologous P501S-transduced fibroblasts. The P501S-specific activity of cell line 3A-1 could be maintained following additional stimulation cycles on autologous B-LCL transduced with P501S. Line 3A-1 was shown to specifically recognize autologous B-LCL transduced to express P501S, but not EGFP-transduced autologous B-LCL, as measured by cytotoxicity assays (<sup>51</sup>Cr release) and interferon-gamma production (Interferon-gamma Elispot; *see* above and Lalvani et al., *J. Exp. Med. 186*:859-865, 1997). The results of these assays are presented in Figures 6A and 6B.

10 EXAMPLE 10

# IDENTIFICATION OF A NATURALLY PROCESSED CTL EPITOPE CONTAINED WITHIN A PROSTATE-SPECIFIC ANTIGEN

The 9-mer peptide p5 (SEQ ID NO: 338) was derived from the P703P antigen (also referred to as P20). The p5 peptide is immunogenic in human HLA-A2 donors and is a naturally processed epitope. Antigen specific human CD8+ T cells can be primed following repeated *in vitro* stimulations with monocytes pulsed with p5 peptide. These CTL specifically recognize p5-pulsed and P703P-transduced target cells in both ELISPOT (as described above) and chromium release assays. Additionally, immunization of HLA-A2Kb transgenic mice with p5 leads to the generation of CTL lines which recognize a variety of HLA-A2Kb or HLA-A2 transduced target cells expressing P703P.

Initial studies demonstrating that p5 is a naturally processed epitope were done using HLA-A2Kb transgenic mice. HLA-A2Kb transgenic mice were immunized subcutaneously in the footpad with 100 µg of p5 peptide together with 140 µg of hepatitis B virus core peptide (a Th peptide) in Freund's incomplete adjuvant. Three weeks post immunization, spleen cells from immunized mice were stimulated *in vitro* with peptide-pulsed LPS blasts. CTL activity was assessed by chromium release assay five days after primary *in vitro* stimulation. Retrovirally transduced cells expressing the control antigen

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P703P and HLA-A2Kb were used as targets. CTL lines that specifically recognized both p5-pulsed targets as well as P703P-expressing targets were identified.

Human *in vitro* priming experiments demonstrated that the p5 peptide is immunogenic in humans. Dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by culturing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, the DC were pulsed with 1 ug/ml p5 peptide and cultured with CD8+ T cell enriched PBMC. CTL lines were restimulated on a weekly basis with p5-pulsed monocytes. Five to six weeks after initiation of the CTL cultures, CTL recognition of p5-pulsed target cells was demonstrated. CTL were additionally shown to recognize human cells transduced to express P703P, demonstrating that p5 is a naturally processed epitope.

Studies identifying a further peptide epitope (referred to as peptide 4) derived from the prostate tumor-specific antigen P703P that is capable of being recognized by CD4 T cells on the surface of cells in the context of HLA class II molecules were carried out as follows. The amino acid sequence for peptide 4 is provided in SEQ ID NO: 781, with the corresponding cDNA sequence being provided in SEQ ID NO: 782.

Twenty 15-mer peptides overlapping by 10 amino acids and derived from the carboxy-terminal fragment of P703P were generated using standard procedures. Dendritic cells (DC) were derived from PBMC of a normal female donor using GM-CSF and IL-4 by standard protocols. CD4 T cells were generated from the same donor as the DC using MACS beads and negative selection. DC were pulsed overnight with pools of the 15-mer peptides, with each peptide at a final concentration of 0.25 microgram/ml. Pulsed DC were washed and plated at 1 x 10<sup>4</sup> cells/well of 96-well V-bottom plates and purified CD4 T cells were added at 1 x 10<sup>5</sup>/well. Cultures were supplemented with 60 ng/ml IL-6 and 10 ng/ml IL-12 and incubated at 37 °C. Cultures were restimulated as above on a weekly basis using DC generated and pulsed as above as antigen presenting cells, supplemented with 5 ng/ml IL-7 and 10 u/ml IL-2. Following 4 *in vitro* stimulation cycles, 96 lines (each line corresponding to one well) were tested for specific proliferation

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and cytokine production in response to the stimulating pools with an irrelevant pool of peptides derived from mammaglobin being used as a control.

One line (referred to as 1-F9) was identified from pool #1 that demonstrated specific proliferation (measured by 3H proliferation assays) and cytokine production (measured by interferon-gamma ELISA assays) in response to pool #1 of P703P peptides. This line was further tested for specific recognition of the peptide pool, specific recognition of individual peptides in the pool, and in HLA mismatch analyses to identify the relevant restricting allele. Line 1-F9 was found to specifically proliferate and produce interferongamma in response to peptide pool #1, and also to peptide 4 (SEQ ID NO: 781). Peptide 4 corresponds to amino acids 126-140 of SEQ ID NO: 327. Peptide titration experiments were conducted to assess the sensitivity of line 1-F9 for the specific peptide. The line was found to specifically respond to peptide 4 at concentrations as low as 0.25 ng/ml, indicating that the T cells are very sensitive and therefore likely to have high affinity for the epitope.

To determine the HLA restriction of the P703P response, a panel of antigen presenting cells (APC) was generated that was partially matched with the donor used to generate the T cells. The APC were pulsed with the peptide and used in proliferation and cytokine assays together with line 1-F9. APC matched with the donor at HLA-DRB0701 and HLA-DQB02 alleles were able to present the peptide to the T cells, indicating that the P703P-specific response is restricted to one of these alleles.

In further studies, twenty-four 15-mer peptides overlapping by 10 amino acids and derived from the N-terminal fragment of P703P (corresponding to amino acids 27-154 of SEQ ID NO: 525) were generated by standard procedures and their ability to be recognized by CD4 cells was determined essentially as described above. DC were pulsed overnight with pools of the peptides with each peptide at a final concentration of 10 microgram/ml. A large number of individual CD4 T cell lines (65/480) demonstrated significant proliferation and cytokine release (IFN-gamma) in response to the P703P peptide pools but not to a control peptide pool. The CD4 T cell lines which demonstrated specific activity were restimulated on the appropriate pool of P703P peptides and reassayed on the individual peptides of each pool as well as a peptide dose titration of the pool of peptides in a IFN-gamma release assay and in a proliferation assay.

Sixteen immunogenic peptides were recognized by the T cells from the entire set of peptide antigens tested. The amino acid sequences of these peptides are provided in SEQ ID NO: 799-814, with the corresponding cDNA sequences being provided in SEQ ID NO: 783-798, respectively. In some cases the peptide reactivity of the T cell line could be mapped to a single peptide, however some could be mapped to more than one peptide in each pool. Those CD4 T cell lines that displayed a representative pattern of recognition from each peptide pool with a reasonable affinity for peptide were chosen for further analysis (I-1A, -6A; II-4C, -5E; III-6E, IV-4B, -3F, -9B, -10F, V-5B, -4D, and -10F). These CD4 T cells lines were restimulated on the appropriate individual peptide and reassayed on autologous DC pulsed with a truncated form of recombinant P703P protein made in E. coli (a.a. 96 - 254 of SEQ ID NO: 525), full-length P703P made in the baculovirus expression system, and a fusion between influenza virus NS1 and P703P made in E. coli. Of the T cell lines tested, line I-1A recognized specifically the truncated form of P703P (E. coli) but no other recombinant form of P703P. This line also recognized the peptide used to elicit the T cells. Line 2-4C recognized the truncated form of P703P (E. coli) and the full length form of P703P made in baculovirus, as well as peptide. The remaining T cell lines tested were either peptide-specific only (II-5E, II-6F, IV-4B, IV-3F, IV-9B, IV-10F, V-5B and V-4D) or were non-responsive to any antigen tested (V-10F). These results demonstrate that the peptide sequence RPLLANDLMLIKLDE (SEQ ID NO: 814; corresponding to a.a. 110-124 of SEQ ID NO: 525) recognized by the T cell line I-1A, and the peptide sequences SVSESDTIRSISIAS (SEQ ID NO: 811; corresponding to a.a. 125-139 of SEQ ID NO: 525) and ISIASQCPTAGNSCL (SEQ ID NO: 810; corresponding to a.a. 135-149 of SEQ ID NO: 525) recognized by the T cell line II-4C may be naturally processed epitopes of the P703P protein.

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#### EXAMPLE 11

### EXPRESSION OF A BREAST TUMOR-DERIVED ANTIGEN IN PROSTATE

Isolation of the antigen B305D from breast tumor by differential display is described in US Patent Application No. 08/700,014, filed August 20, 1996. Several different splice forms of this antigen were isolated. The determined cDNA sequences for these splice forms are provided in SEQ ID NO: 366-375, with the predicted amino acid sequences corresponding to the sequences of SEQ ID NO: 292, 298 and 301-303 being provided in SEQ ID NO: 299-306, respectively. In further studies, a splice variant of the cDNA sequence of SEQ ID NO: 366 was isolated which was found to contain an additional guanine residue at position 884 (SEQ ID NO: 530), leading to a frameshift in the open reading frame. The determined DNA sequence of this ORF is provided in SEQ ID NO: 531. This frameshift generates a protein sequence (provided in SEQ ID NO: 532) of 293 amino acids that contains the C-terminal domain common to the other isoforms of B305D but that differs in the N-terminal region.

The expression levels of B305D in a variety of tumor and normal tissues were examined by real time PCR and by Northern analysis. The results indicated that B305D is highly expressed in breast tumor, prostate tumor, normal prostate and normal testes, with expression being low or undetectable in all other tissues examined (colon tumor, lung tumor, ovary tumor, and normal bone marrow, colon, kidney, liver, lung, ovary, skin, small intestine, stomach). Using real-time PCR on a panel of prostate tumors, expression of B305D in prostate tumors was shown to increase with increasing Gleason grade, demonstrating that expression of B305D increases as prostate cancer progresses.

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### EXAMPLE 12

# GENERATION OF HUMAN CTL IN VITRO USING WHOLE GENE PRIMING AND STIMULATION TECHNIQUES WITH PROSTATE-SPECIFIC ANTIGEN

Using in vitro whole-gene priming with P501S-vaccinia infected DC (see, for example, Yee et al, The Journal of Immunology, 157(9):4079-86, 1996), human CTL lines were derived that specifically recognize autologous fibroblasts transduced with P501S (also known as L1-12), as determined by interferon-y ELISPOT analysis as described above. Using a panel of HLA-mismatched B-LCL lines transduced with P501S, these CTL lines were shown to be likely restricted to HLAB class I allele. Specifically, dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by growing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, DC were infected overnight with recombinant P501S vaccinia virus at a multiplicity of infection (M.O.I) of five, and matured overnight by the addition of 3 µg/ml CD40 ligand. Virus was inactivated by UV irradiation. CD8+ T cells were isolated using a magnetic bead system, and priming cultures were initiated using standard culture techniques. Cultures were restimulated every 7-10 days using autologous primary fibroblasts retrovirally transduced with P501S and Following four stimulation cycles, CD8+ T cell lines were identified that CD80. specifically produced interferon-y when stimulated with P501S and CD80-transduced autologous fibroblasts. A panel of HLA-mismatched B-LCL lines transduced with P501S were generated to define the restriction allele of the response. By measuring interferon-γ in an ELISPOT assay, the P501S specific response was shown to be likely restricted by HLA B alleles. These results demonstrate that a CD8+ CTL response to P501S can be elicited.

To identify the epitope(s) recognized, cDNA encoding P501S was fragmented by various restriction digests, and sub-cloned into the retroviral expression vector pBIB-KS. Retroviral supernatants were generated by transfection of the helper packaging line Phoenix-Ampho. Supernatants were then used to transduce Jurkat/A2Kb cells for CTL screening. CTL were screened in IFN-gamma ELISPOT assays against these

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A2Kb targets transduced with the "library" of P501S fragments. Initial positive fragments P501S/H3 and P501S/F2 were sequenced and found to encode amino acids 106-553 and amino acids 136-547, respectively, of SEQ ID NO: 113. A truncation of H3 was made to encode amino acid residues 106-351 of SEQ ID NO: 113, which was unable to stimulate the CTL, thus localizing the epitope to amino acid residues 351-547. Additional fragments encoding amino acids 1-472 (Fragment A) and amino acids 1-351 (Fragment B) were also constructed. Fragment A but not Fragment B stimulated the CTL thus localizing the epitope to amino acid residues 351-472. Overlapping 20-mer and 18-mer peptides representing this region were tested by pulsing Jurkat/A2Kb cells versus CTL in an IFN-gamma assay. Only peptides P501S-369(20) and P501S-369(18) stimulated the CTL. Nine-mer and 10-mer peptides representing this region were synthesized and similarly tested. Peptide P501S-370 (SEQ ID NO: 539) was the minimal 9-mer giving a strong response. Peptide P501S-376 (SEQ ID NO: 540) also gave a weak response, suggesting that it might represent a cross-reactive epitope.

In subsequent studies, the ability of primary human B cells transduced with P501S to prime MHC class I-restricted, P501S-specific, autologous CD8 T cells was examined. Primary B cells were derived from PBMC of a homozygous HLA-A2 donor by culture in CD40 ligand and IL-4, transduced at high frequency with recombinant P501S in the vector pBIB, and selected with blastocidin-S. For in vitro priming, purified CD8+ T cells were cultured with autologous CD40 ligand + IL-4 derived, P501S-transduced B cells in a 96-well microculture format. These CTL microcultures were re-stimulated with P501S-transduced B cells and then assayed for specificity. Following this initial screen, microcultures with significant signal above background were cloned on autologous EBVtransformed B cells (BLCL), also transduced with P501S. Using IFN-gamma ELISPOT for detection, several of these CD8 T cell clones were found to be specific for P501S, as demonstrated by reactivity to BLCL/P501S but not BLCL transduced with control antigen. It was further demonstrated that the anti-P501S CD8 T cell specificity is HLA-A2restricted. First, antibody blocking experiments with anti-HLA-A,B,C monoclonal antibody (W6.32), anti-HLA-B,C monoclonal antibody (B1.23.2) and a control monoclonal antibody showed that only the anti-HLA-A,B,C antibody blocked recognition of P501S-expressing autologous BLCL. Secondly, the anti-P501S CTL also recognized an HLA-A2 matched, heterologous BLCL transduced with P501S, but not the corresponding EGFP transduced control BLCL.

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#### **EXAMPLE 13**

# IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS By Microarray Analysis

This Example describes the isolation of certain prostate-specific polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 372 clones were identified, and 319 were successfully sequenced. Table I presents a summary of these clones, which are shown in SEQ ID NOs:385-400. Of these sequences SEQ ID NOs:386, 389, 390 and 392 correspond to novel genes, and SEQ ID NOs: 393 and 396 correspond to previously identified sequences. The others (SEQ ID NOs:385, 387, 388, 391, 394, 395 and 397-400) correspond to known sequences, as shown in Table I.

### Table I

### Summary of Prostate Tumor Antigens

Known Genes	Previously Identified Genes	Novel Genes
T-cell gamma chain	P504S	23379 (SEQ ID NO:389)
Kallikrein	P1000C	23399 (SEQ ID NO:392)
Vector	P501S	23320 (SEQ ID NO:386)
CGI-82 protein mRNA (23319; SEQ ID NO:385)	P503S	23381 (SEQ ID NO:390)
PSA	P510S	
Ald. 6 Dehyd.	P784P	
L-iditol-2 dehydrogenase (23376; SEQ ID NO:388)	P502S	
Ets transcription factor PDEF (22672; SEQ ID NO:398)	P706P	
hTGR (22678; SEQ ID NO:399)	19142.2, bangur.seq (22621; SEQ ID NO:396)	
KIAA0295(22685; SEQ ID NO:400)	5566.1 Wang (23404; SEQ ID NO:393)	
Prostatic Acid Phosphatase(22655; SEQ ID NO:397)	P712P	
transglutaminase (22611; SEQ ID NO:395)	P778P	
HDLBP (23508; SEQ ID NO:394)		
CGI-69 Protein(23367; SEQ ID NO:387)		
KIAA0122(23383; SEQ ID NO:391)		
TEEG		
HDLBP (23508; SEQ ID NO:394)  CGI-69 Protein(23367; SEQ ID NO:387)  KIAA0122(23383; SEQ ID NO:391)	P778P	

CGI-82 showed 4.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 43% of prostate tumors, 25% normal

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prostate, not detected in other normal tissues tested. L-iditol-2 dehydrogenase showed 4.94 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 90% of prostate tumors, 100% of normal prostate, and not detected in other normal tissues tested. Ets transcription factor PDEF showed 5.55 fold overexpression in prostate tissues as compared to other normal tissues tested. It was overexpressed in 47% prostate tumors, 25% normal prostate and not detected in other normal tissues tested. hTGR1 showed 9.11 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 63% of prostate tumors and is not detected in normal tissues tested including normal prostate. KIAA0295 showed 5.59 fold over-expression in prostate tissues as compared to other normal tissues tested. It was overexpressed in 47% of prostate tumors, low to undetectable in normal tissues tested including normal prostate tissues. Prostatic acid phosphatase showed 9.14 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 67% of prostate tumors, 50% of normal prostate, and not detected in other normal tissues tested. Transglutaminase showed 14.84 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 30% of prostate tumors, 50% of normal prostate, and is not detected in other normal tissues tested. High density lipoprotein binding protein (HDLBP) showed 28.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% of normal prostate, and is undetectable in all other normal tissues tested. CGI-69 showed 3.56 fold over-expression in prostate tissues as compared to other normal tissues tested. It is a low abundant gene, detected in more than 90% of prostate tumors, and in 75% normal prostate tissues. The expression of this gene in normal tissues was very low. KIAA0122 showed 4.24 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 57% of prostate tumors, it was undetectable in all normal tissues tested including normal prostate tissues. 19142.2 bangur showed 23.25 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors and 100% of normal prostate. It was undetectable in other normal tissues tested. 5566.1 Wang showed 3.31 fold overexpression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% normal prostate and was also over-expressed in normal bone marrow, pancreas, and activated PBMC. Novel clone 23379 (also referred to as P553S) showed 4.86 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in 97% of prostate tumors and 75% normal prostate and is undetectable in all other normal tissues tested. Novel clone 23399 showed 4.09 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 27% of prostate tumors and was undetectable in all normal tissues tested including normal prostate tissues. Novel clone 23320 showed 3.15 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in all prostate tumors and 50% of normal prostate tissues. It was also expressed in normal colon and trachea. Other normal tissues do not express this gene at high level.

Subsequent full-length cloning studies on P553S, using standard techniques, revealed that this clone is an incomplete spliced form of P501S. The determined cDNA sequences for four splice variants of P553S are provided in SEQ ID NO: 702-705. An amino acid sequence encoded by SEQ ID NO: 705 is provided in SEQ ID NO: 706. The cDNA sequence of SEQ ID NO: 702 was found to contain two open reading frames (ORFs). The amino acid sequences encoded by these two ORFs are provided in SEQ ID NO: 707 and 708.

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#### **EXAMPLE 14**

## IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS BY ELECTRONIC SUBTRACTION

This Example describes the use of an electronic subtraction technique to identify prostate-specific antigens.

Potential prostate-specific genes present in the GenBank human EST database were identified by electronic subtraction (similar to that described by Vasmatizis et al., *Proc. Natl. Acad. Sci. USA 95*:300-304, 1998). The sequences of EST clones

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(43,482) derived from various prostate libraries were obtained from the GenBank public human EST database. Each prostate EST sequence was used as a query sequence in a BLASTN (National Center for Biotechnology Information) search against the human EST database. All matches considered identical (length of matching sequence >100 base pairs, density of identical matches over this region > 70%) were grouped (aligned) together in a cluster. Clusters containing more than 200 ESTs were discarded since they probably represented repetitive elements or highly expressed genes such as those for ribosomal proteins. If two or more clusters shared common ESTs, those clusters were grouped together into a "supercluster," resulting in 4,345 prostate superclusters.

Records for the 479 human cDNA libraries represented in the GenBank release were downloaded to create a database of these cDNA library records. These 479 cDNA libraries were grouped into three groups: Plus (normal prostate and prostate tumor libraries, and breast cell line libraries, in which expression was desired), Minus (libraries from other normal adult tissues, in which expression was not desirable), and Other (libraries from fetal tissue, infant tissue, tissues found only in women, non-prostate tumors and cell lines other than prostate cell lines, in which expression was considered to be irrelevant). A summary of these library groups is presented in Table II.

<u>Table II</u>

<u>Prostate cDNA Libraries and ESTs</u>

Library	# of Libraries	# of ESTs
Plus	25	43,482
Normal	11	18,875
Tumor	11	21,769
Cell lines	3	2,838
Minus	166	
Other	287	

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Each supercluster was analyzed in terms of the ESTs within the supercluster. The tissue source of each EST clone was noted and used to classify the superclusters into four groups: Type 1- EST clones found in the Plus group libraries only; no expression detected in Minus or Other group libraries; Type 2- EST clones derived from the Plus and Other group libraries only; no expression detected in the Minus group; Type 3- EST clones derived from the Plus, Minus and Other group libraries, but the number of ESTs derived from the Plus group is higher than in either the Minus or Other groups; and Type 4- EST clones derived from Plus, Minus and Other group libraries, but the number derived from the Plus group is higher than the number derived from the Minus group. This analysis identified 4,345 breast clusters (*see* Table III). From these clusters, 3,172 EST clones were ordered from Research Genetics, Inc., and were received as frozen glycerol stocks in 96-well plates.

<u>Table III</u>

<u>Prostate Cluster Summary</u>

Туре	# of Superclusters	# of ESTs Ordered
1	688	677
2	2899	2484
3	85	11
4	673	0
Total	4345	3172

The EST clone inserts were PCR-amplified using amino-linked PCR primers for Synteni microarray analysis. When more than one PCR product was obtained for a particular clone, that PCR product was not used for expression analysis. In total, 2,528 clones from the electronic subtraction method were analyzed by microarray analysis to identify electronic subtraction breast clones that had high levels of tumor vs. normal

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tissue mRNA. Such screens were performed using a Synteni (Palo Alto, CA) microarray, according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Within these analyses, the clones were arrayed on the chip, which was then probed with fluorescent probes generated from normal and tumor prostate cDNA, as well as various other normal tissues. The slides were scanned and the fluorescence intensity was measured.

Clones with an expression ratio greater than 3 (*i.e.*, the level in prostate tumor and normal prostate mRNA was at least three times the level in other normal tissue mRNA) were identified as prostate tumor-specific sequences (Table IV). The sequences of these clones are provided in SEQ ID NO: 401-453, with certain novel sequences shown in SEQ ID NO: 407, 413, 416-419, 422, 426, 427 and 450.

<u>Table IV</u>

Prostate-tumor Specific Clones

SEQ ID NO.	Sequence Designation	Comments
401	22545	previously identified P1000C
402	22547	previously identified P704P
403	22548	known
404	22550	known
405	22551	PSA
406	22552	prostate secretory protein 94
407	22553	novel
408	22558	previously identified P509S
409	22562	glandular kallikrein
410	22565	previously identified P1000C
411	22567	PAP
412	22568	B1006C (breast tumor antigen)
413	22570	novel
414	22571	PSA
415	22572	previously identified P706P
416	22573	novel
417	22574	novel

418	22575	novel	
419	22580	novel	
420	22581	PAP	
421	22582	prostatic secretory protein 94	
422	22583	novel	
423	22584	prostatic secretory protein 94	
424	22585	prostatic secretory protein 94	
425	22586	known	
426	22587	novel	
427	22588	novel	
428	22589	PAP	
429	22590	known	
430	22591	PSA	
431	22592	known	
432	22593	Previously identified P777P	
433	22594	T cell receptor gamma chain	
434	22595	Previously identified P705P	
435	22596	Previously identified P707P	
436	22847	PAP	
437	22848	known	
438	22849	prostatic secretory protein 57	
439	22851	, PAP	
440	22852	PAP	
441	22853	PAP	
442	22854	previously identified P509S	
443	22855	previously identified P705P	
444	22856	previously identified P774P	
445	22857	PSA	
446	23601	previously identified P777P	
447	23602	PSA	
448	23605	PSA	
449	23606	PSA	
450	23612	novel	
451	23614	PSA	
452	23618	previously identified P1000C	
453	23622	previously identified P705P	

Further studies on the clone of SEQ ID NO: 407 (also referred to as P1020C) led to the isolation of an extended cDNA sequence provided in SEQ ID NO: 591. This extended cDNA sequence was found to contain an open reading frame that encodes

the predicted amino acid sequence of SEQ ID NO: 592. The P1020C cDNA and amino acid sequences were found to show some similarity to the human endogenous retroviral HERV-K pol gene and protein.

5 EXAMPLE 15

FURTHER IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of additional prostate-specific polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 142 clones were identified and sequenced. Certain of these clones are shown in SEQ ID NO: 454-467. Of these sequences, SEQ ID NO: 459-461 represent novel genes. The others (SEQ ID NO: 454-458 and 461-467) correspond to known sequences.

### **EXAMPLE 16**

FURTHER CHARACTERIZATION OF PROSTATE-SPECIFIC ANTIGEN P710P

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This Example describes the full length cloning of P710P.

The prostate cDNA library described above was screened with the P710P fragment described above. One million colonies were plated on LB/Ampicillin plates. Nylon membrane filters were used to lift these colonies, and the cDNAs picked up by these filters were then denatured and cross-linked to the filters by UV light. The P710P fragment was radiolabeled and used to hybridize with the filters. Positive cDNA clones were selected and their cDNAs recovered and sequenced by an automatic Perkin Elmer/Applied Biosystems Division Sequencer. Four sequences were obtained, and are presented in SEQ ID NO: 468-471. These sequences appear to represent different splice variants of the

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P710P gene. Subsequent comparison of the cDNA sequences of P710P with those in Genbank releaved homology to the DD3 gene (Genbank accession numbers AF103907 & AF103908). The cDNA sequence of DD3 is provided in SEQ ID NO: 690.

5 EXAMPLE 17

PROTEIN EXPRESSION OF THE PROSTATE-SPECIFIC ANTIGEN P501S

This example describes the expression and purification of the prostate-specific antigen P501S in *E. coli*, baculovirus and mammalian cells.

### 10 A) EXPRESSION IN E. COLI

Expression of the full-length form of P501S was attempted by first cloning P501S without the leader sequence (amino acids 36-553 of SEQ ID NO: 113) downstream of the first 30 amino acids of the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 484) in pET17b. Specifically, P501S DNA was used to perform PCR using the primers AW025 (SEQ ID NO: 485) and AW003 (SEQ ID NO: 486). AW025 is a sense cloning primer that contains a HindIII site. AW003 is an antisense cloning primer that contains an EcoRI site. DNA amplification was performed using 5 μl 10X Pfu buffer, 1 μl 20 mM dNTPs, 1 μl each of the PCR primers at 10 μM concentration, 40 μl water, 1 μl Pfu DNA polymerase (Stratagene, La Jolla, CA) and 1 μl DNA at 100 ng/μl. Denaturation at 95°C was performed for 30 sec, followed by 10 cycles of 95°C for 30 sec, 60°C for 1 min and by 72°C for 3 min. 20 cycles of 95°C for 30 sec, 65°C for 1 min and by 72°C for 3 min, and lastly by 1 cycle of 72°C for 10 min. The PCR product was cloned to Ra12m/pET17b using HindIII and EcoRI. The sequence of the resulting fusion construct (referred to as Ra12-P501S-F) was confirmed by DNA sequencing.

The fusion construct was transformed into BL21(DE3)pLysE, pLysS and CodonPlus *E. coli* (Stratagene) and grown overnight in LB broth with kanamycin. The resulting culture was induced with IPTG. Protein was transferred to PVDF membrane and blocked with 5% non-fat milk (in PBS-Tween buffer), washed three times and incubated

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with mouse anti-His tag antibody (Clontech) for 1 hour. The membrane was washed 3 times and probed with HRP-Protein A (Zymed) for 30 min. Finally, the membrane was washed 3 times and developed with ECL (Amersham). No expression was detected by Western blot. Similarly, no expression was detected by Western blot when the Ra12-P501S-F fusion was used for expression in BL21CodonPlus by CE6 phage (Invitrogen).

An N-terminal fragment of P501S (amino acids 36-325 of SEQ ID NO: 113) was cloned down-stream of the first 30 amino acids of the *M. tuberculosis* antigen Ra12 in pET17b as follows. P501S DNA was used to perform PCR using the primers AW025 (SEQ ID NO: 485) and AW027 (SEQ ID NO: 487). AW027 is an antisense cloning primer that contains an EcoRI site and a stop codon. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the HindIII and EcoRI sites. The fusion construct (referred to as Ra12-P501S-N) was confirmed by DNA sequencing.

The Ra12-P501S-N fusion construct was used for expression in BL21(DE3)pLysE, pLysS and CodonPlus, essentially as described above. Using Western blot analysis, protein bands were observed at the expected molecular weight of 36 kDa. Some high molecular weight bands were also observed, probably due to aggregation of the recombinant protein. No expression was detected by Western blot when the Ra12-P501S-F fusion was used for expression in BL21CodonPlus by CE6 phage.

A fusion construct comprising a C-terminal portion of P501S (amino acids 257-553 of SEQ ID NO: 113) located down-stream of the first 30 amino acids of the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 484) was prepared as follows. P501S DNA was used to perform PCR using the primers AW026 (SEQ ID NO: 488) and AW003 (SEQ ID NO: 486). AW026 is a sense cloning primer that contains a HindIII site. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the HindIII and EcoRI sites. The sequence for the fusion construct (referred to as Ra12-P501S-C) was confirmed.

The Ra12-P501S-C fusion construct was used for expression in BL21(DE3)pLysE, pLysS and CodonPlus, as described above. A small amount of protein

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was detected by Western blot, with some molecular weight aggregates also being observed. Expression was also detected by Western blot when the Ra12-P501S-C fusion was used for expression in BL21CodonPlus induced by CE6 phage.

### **B)** EXPRESSION OF P501S IN BACULOVIRUS

The Bac-to-Bac baculovirus expression system (BRL Life Technologies, Inc.) was used to express P501S protein in insect cells. Full-length P501S (SEQ ID NO: 113) was amplified by PCR and cloned into the XbaI site of the donor plasmid pFastBacI. The recombinant bacmid and baculovirus were prepared according to the manufacturer's instructions. The recombinant baculovirus was amplified in Sf9 cells and the high titer viral stocks were utilized to infect High Five cells (Invitrogen) to make the recombinant protein. The identity of the full-length protein was confirmed by N-terminal sequencing of the recombinant protein and by Western blot analysis (Figure 7). Specifically, 0.6 million High Five cells in 6-well plates were infected with either the unrelated control virus BV/ECD\_PD (lane 2), with recombinant baculovirus for P501S at different amounts or MOIs (lanes 4-8), or were uninfected (lane 3). Cell lysates were run on SDS-PAGE under reducing conditions and analyzed by Western blot with the anti-P501S monoclonal antibody P501S-10E3-G4D3 (prepared as described below). Lane 1 is the biotinylated protein molecular weight marker (BioLabs).

The localization of recombinant P501S in the insect cells was investigated as follows. The insect cells overexpressing P501S were fractionated into fractions of nucleus, mitochondria, membrane and cytosol. Equal amounts of protein from each fraction were analyzed by Western blot with a monoclonal antibody against P501S. Due to the scheme of fractionation, both nucleus and mitochondria fractions contain some plasma membrane components. However, the membrane fraction is basically free from mitochondria and nucleus. P501S was found to be present in all fractions that contain the membrane component, suggesting that P501S may be associated with plasma membrane of the insect cells expressing the recombinant protein.

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### C) EXPRESSION OF P501S IN MAMMALIAN CELLS

Full-length P501S (553AA) was cloned into various mammalian expression vectors, including pCEP4 (Invitrogen), pVR1012 (Vical, San Diego, CA) and a modified form of the retroviral vector pBMN, referred to as pBIB. Transfection of P501S/pCEP4 and P501S/pVR1012 into HEK293 fibroblasts was carried out using the Fugene transfection reagent (Boehringer Mannheim). Briefly, 2 ul of Fugene reagent was diluted into 100 ul of serum-free media and incubated at room temperature for 5-10 min. This mixture was added to 1 ug of P501S plasmid DNA, mixed briefly and incubated for 30 minutes at room temperature. The Fugene/DNA mixture was added to cells and incubated for 24-48 hours. Expression of recombinant P501S in transfected HEK293 fibroblasts was detected by means of Western blot employing a monoclonal antibody to P501S.

Transfection of p501S/pCEP4 into CHO-K cells (American Type Culture Collection, Rockville, MD) was carried out using GenePorter transfection reagent (Gene Therapy Systems, San Diego, CA). Briefly, 15 µl of GenePorter was diluted in 500 µl of serum-free media and incubated at room temperature for 10 min. The GenePorter/media mixture was added to 2 µg of plasmid DNA that was diluted in 500 µl of serum-free media, mixed briefly and incubated for 30 min at room temperature. CHO-K cells were rinsed in PBS to remove serum proteins, and the GenePorter/DNA mix was added and incubated for 5 hours. The transfected cells were then fed an equal volume of 2x media and incubated for 24-48 hours.

FACS analysis of P501S transiently infected CHO-K cells, demonstrated surface expression of P501S. Expression was detected using rabbit polyclonal antisera raised against a P501S peptide, as described below. Flow cytometric analysis was performed using a FaCScan (Becton Dickinson), and the data were analyzed using the Cell Quest program.

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### **EXAMPLE 18**

## PREPARATION AND CHARACTERIZATION OF ANTIBODIES AGAINST PROSTATE-SPECIFIC POLYPEPTIDES

# 5 <u>A) Preparation and Characterization of Polyclonal Antibodies against</u> P703P, P504S and P509S

Polyclonal antibodies against P703P, P504S and P509S were prepared as follows.

Each prostate tumor antigen expressed in an E. coli recombinant expression system was grown overnight in LB broth with the appropriate antibiotics at 37°C in a shaking incubator. The next morning, 10 ml of the overnight culture was added to 500 ml to 2x YT plus appropriate antibiotics in a 2L-baffled Erlenmeyer flask. When the Optical Density (at 560 nm) of the culture reached 0.4-0.6, the cells were induced with IPTG (1 mM). Four hours after induction with IPTG, the cells were harvested by centrifugation. The cells were then washed with phosphate buffered saline and centrifuged again. The supernatant was discarded and the cells were either frozen for future use or immediately processed. Twenty ml of lysis buffer was added to the cell pellets and vortexed. To break open the E. coli cells, this mixture was then run through the French Press at a pressure of 16,000 psi. The cells were then centrifuged again and the supernatant and pellet were checked by SDS-PAGE for the partitioning of the recombinant protein. For proteins that localized to the cell pellet, the pellet was resuspended in 10 mM Tris pH 8.0, 1% CHAPS and the inclusion body pellet was washed and centrifuged again. This procedure was repeated twice more. The washed inclusion body pellet was solubilized with either 8 M urea or 6 M guanidine HCl containing 10 mM Tris pH 8.0 plus 10 mM imidazole. The solubilized protein was added to 5 ml of nickel-chelate resin (Qiagen) and incubated for 45 min to 1 hour at room temperature with continuous agitation. After incubation, the resin and protein mixture were poured through a disposable column and the flow through was collected. The column was then washed with 10-20 column volumes of the solubilization

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buffer. The antigen was then eluted from the column using 8M urea, 10 mM Tris pH 8.0 and 300 mM imidazole and collected in 3 ml fractions. A SDS-PAGE gel was run to determine which fractions to pool for further purification.

As a final purification step, a strong anion exchange resin such as HiPrepQ (Biorad) was equilibrated with the appropriate buffer and the pooled fractions from above were loaded onto the column. Each antigen was eluted off the column with a increasing salt gradient. Fractions were collected as the column was run and another SDS-PAGE gel was run to determine which fractions from the column to pool. The pooled fractions were dialyzed against 10 mM Tris pH 8.0. The proteins were then vialed after filtration through a 0.22 micron filter and the antigens were frozen until needed for immunization. 10

Four hundred micrograms of each prostate antigen was combined with 100 micrograms of muramyldipeptide (MDP). Every four weeks rabbits were boosted with 100 micrograms mixed with an equal volume of Incomplete Freund's Adjuvant (IFA). Seven days following each boost, the animal was bled. Sera was generated by incubating the blood at 4°C for 12-4 hours followed by centrifugation.

Ninety-six well plates were coated with antigen by incubating with 50 microliters (typically 1 microgram) of recombinant protein at 4 °C for 20 hours. 250 microliters of BSA blocking buffer was added to the wells and incubated at room temperature for 2 hours. Plates were washed 6 times with PBS/0.01% Tween. Rabbit sera was diluted in PBS. Fifty microliters of diluted sera was added to each well and incubated at room temperature for 30 min. Plates were washed as described above before 50 microliters of goat anti-rabbit horse radish peroxidase (HRP) at a 1:10000 dilution was added and incubated at room temperature for 30 min. Plates were again washed as described above and 100 microliters of TMB microwell peroxidase substrate was added to each well. Following a 15 min incubation in the dark at room temperature, the colorimetric reaction was stopped with 100 microliters of 1N H<sub>2</sub>SO<sub>4</sub> and read immediately at 450 nm. All polyclonal antibodies showed immunoreactivity to the appropriate antigen.

### B) PREPARATION AND CHARACTERIZATION OF ANTIBODIES AGAINST P501S

A murine monoclonal antibody directed against the carboxy-terminus of the prostate-specific antigen P501S was prepared as follows.

A truncated fragment of P501S (amino acids 355-526 of SEQ ID NO: 113) was generated and cloned into the pET28b vector (Novagen) and expressed in *E. coli* as a thioredoxin fusion protein with a histidine tag. The trx-P501S fusion protein was purified by nickel chromatography, digested with thrombin to remove the trx fragment and further purified by an acid precipitation procedure followed by reverse phase HPLC.

Mice were immunized with truncated P501S protein. Serum bleeds from mice that potentially contained anti-P501S polyclonal sera were tested for P501S-specific reactivity using ELISA assays with purified P501S and trx-P501S proteins. Serum bleeds that appeared to react specifically with P501S were then screened for P501S reactivity by Western analysis. Mice that contained a P501S-specific antibody component were sacrificed and spleen cells were used to generate anti-P501S antibody producing hybridomas using standard techniques. Hybridoma supernatants were tested for P501S-specific reactivity initially by ELISA, and subsequently by FACS analysis of reactivity with P501S transduced cells. Based on these results, a monoclonal hybridoma referred to as 10E3 was chosen for further subcloning. A number of subclones were generated, tested for specific reactivity to P501S using ELISA and typed for IgG isotype. The results of this analysis are shown below in Table V. Of the 16 subclones tested, the monoclonal antibody 10E3-G4-D3 was selected for further study.

Table V

Isotype analysis of murine anti-P501S monoclonal antibodies

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Hybridoma clone	Isotype	Estimated [Ig] in supernatant (µg/ml)
4D11	IgG1	14.6
1G1	IgG1	0.6
4F6	IgG1	72
4H5	IgG1	13.8
4H5-E12	IgG1	10.7

Hybridoma clone	Isotype	Estimated [Ig] in supernatant (µg/ml)
4H5-EH2	IgG1	9.2
4H5-H2-A10	IgG1	10
4H5-H2-A3	IgG1	12.8
4H5-H2-A10-G6	IgG1	13.6
4H5-H2-B11	IgG1	12.3
10E3	IgG2a	3.4
10E3-D4	IgG2a	3.8
10E3-D4-G3	IgG2a	9.5
10E3-D4-G6	IgG2a	10.4
10E3-E7	IgG2a	6.5
8H12	IgG2a	0.6

The specificity of 10E3-G4-D3 for P501S was examined by FACS analysis. Specifically, cells were fixed (2% formaldehyde, 10 minutes), permeabilized (0.1% saponin, 10 minutes) and stained with 10E3-G4-D3 at 0.5 – 1 μg/ml, followed by incubation with a secondary, FITC-conjugated goat anti-mouse Ig antibody (Pharmingen, San Diego, CA). Cells were then analyzed for FITC fluorescence using an Excalibur fluorescence activated cell sorter. For FACS analysis of transduced cells, B-LCL were retrovirally transduced with P501S. For analysis of infected cells, B-LCL were infected with a vaccinia vector that expresses P501S. To demonstrate specificity in these assays, B-LCL transduced with a different antigen (P703P) and uninfected B-LCL vectors were utilized. 10E3-G4-D3 was shown to bind with P501S-transduced B-LCL and also with P501S-infected B-LCL, but not with either uninfected cells or P703P-transduced cells.

To determine whether the epitope recognized by 10E3-G4-D3 was found on the surface or in an intracellular compartment of cells, B-LCL were transduced with P501S or HLA-B8 as a control antigen and either fixed and permeabilized as described above or directly stained with 10E3-G4-D3 and analyzed as above. Specific recognition of P501S by 10E3-G4-D3 was found to require permeabilization, suggesting that the epitope recognized by this antibody is intracellular.

The reactivity of 10E3-G4-D3 with the three prostate tumor cell lines

20 Lncap, PC-3 and DU-145, which are known to express high, medium and very low levels
of P501S, respectively, was examined by permeabilizing the cells and treating them as

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described above. Higher reactivity of 10E3-G4-D3 was seen with Lncap than with PC-3, which in turn showed higher reactivity that DU-145. These results are in agreement with the real time PCR and demonstrate that the antibody specifically recognizes P501S in these tumor cell lines and that the epitope recognized in prostate tumor cell lines is also intracellular.

Specificity of 10E3-G4-D3 for P501S was also demonstrated by Western blot analysis. Lysates from the prostate tumor cell lines Lncap, DU-145 and PC-3, from P501S-transiently transfected HEK293 cells, and from non-transfected HEK293 cells were generated. Western blot analysis of these lysates with 10E3-G4-D3 revealed a 46 kDa immunoreactive band in Lncap, PC-3 and P501S-transfected HEK cells, but not in DU-145 cells or non-transfected HEK293 cells. P501S mRNA expression is consistent with these results since semi-quantitative PCR analysis revealed that P501S mRNA is expressed in Lncap, to a lesser but detectable level in PC-3 and not at all in DU-145 cells. Bacterially expressed and purified recombinant P501S (referred to as P501SStr2) was recognized by 10E3-G4-D3 (24 kDa), as was full-length P501S that was transiently expressed in HEK293 cells using either the expression vector VR1012 or pCEP4. Although the predicted molecular weight of P501S is 60.5 kDa, both transfected and "native" P501S run at a slightly lower mobility due to its hydrophobic nature.

Immunohistochemical analysis was performed on prostate tumor and a panel of normal tissue sections (prostate, adrenal, breast, cervix, colon, duodenum, gall bladder, ileum, kidney, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis). Tissue samples were fixed in formalin solution for 24 hours and embedded in paraffin before being sliced into 10 micron sections. Tissue sections were permeabilized and incubated with 10E3-G4-D3 antibody for 1 hr. HRP-labeled anti-mouse followed by incubation with DAB chromogen was used to visualize P501S immunoreactivity. P501S was found to be highly expressed in both normal prostate and prostate tumor tissue but was not detected in any of the other tissues tested.

To identify the epitope recognized by 10E3-G4-D3, an epitope mapping approach was pursued. A series of 13 overlapping 20-21 mers (5 amino acid overlap; SEQ

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ID NO: 489-501) was synthesized that spanned the fragment of P501S used to generate 10E3-G4-D3. Flat bottom 96 well microtiter plates were coated with either the peptides or the P501S fragment used to immunize mice, at 1 microgram/ml for 2 hours at 37 °C. Wells were then aspirated and blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature, and subsequently washed in PBS containing 0.1% Tween 20 (PBST). Purified antibody 10E3-G4-D3 was added at 2 fold dilutions (1000 ng – 16 ng) in PBST and incubated for 30 minutes at room temperature. This was followed by washing 6 times with PBST and subsequently incubating with HRP-conjugated donkey anti-mouse IgG (H+L)Affinipure F(ab') fragment (Jackson Immunoresearch, West Grove, PA) at 1:20000 for 30 minutes. Plates were then washed and incubated for 15 minutes in tetramethyl benzidine. Reactions were stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using an ELISA plate reader. As shown in Fig. 8, reactivity was seen with the peptide of SEO ID NO: 496 (corresponding to amino acids 439-459 of P501S) and with the P501S fragment but not with the remaining peptides, demonstrating that the epitope recognized by 10E3-G4-D3 is localized to amino acids 439-459 of SEO ID NO: 113.

In order to further evaluate the tissue specificity of P501S, multi-array immunohistochemical analysis was performed on approximately 4700 different human tissues encompassing all the major normal organs as well as neoplasias derived from these tissues. Sixty-five of these human tissue samples were of prostate origin. Tissue sections 0.6 mm in diameter were formalin-fixed and paraffin embedded. Samples were pretreated with HIER using 10 mM citrate buffer pH 6.0 and boiling for 10 min. Sections were stained with 10E3-G4-D3 and P501S immunoreactivity was visualized with HRP. All the 65 prostate tissues samples (5 normal, 55 untreated prostate tumors, 5 hormone refractory prostate tumors) were positive, showing distinct perinuclear staining. All other tissues examined were negative for P501S expression.

### C) PREPARATION AND CHARACTERIZATION OF ANTIBODIES AGAINST P503S

A fragment of P503S (amino acids 113-241 of SEQ ID NO: 114) was expressed and purified from bacteria essentially as described above for P501S and used to immunize both rabbits and mice. Mouse monoclonal antibodies were isolated using standard hybridoma technology as described above. Rabbit monoclonal antibodies were isolated using Selected Lymphocyte Antibody Method (SLAM) technology at Immgenics Pharmaceuticals (Vancouver, BC, Canada). Table VI, below, lists the monoclonal antibodies that were developed against P503S.

10 <u>Table VI</u>

Antibody	Species
20D4	Rabbit
JA1	Rabbit
1A4	Mouse
1C3	Mouse
1C9	Mouse
1D12	Mouse
2A11	Mouse
2H9	Mouse
4H7	Mouse
8A8	Mouse
8D10	Mouse
9C12	Mouse
6D12	Mouse

The DNA sequences encoding the complementarity determining regions (CDRs) for the rabbit monoclonal antibodies 20D4 and JA1 were determined and are provided in SEQ ID NO: 502 and 503, respectively.

In order to better define the epitope binding region of each of the antibodies, a series of overlapping peptides were generated that span amino acids 109-213 of SEQ ID NO: 114. These peptides were used to epitope map the anti-P503S monoclonal antibodies by ELISA as follows. The recombinant fragment of P503S that was employed as the

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immunogen was used as a positive control. Ninety-six well microtiter plates were coated with either peptide or recombinant antigen at 20 ng/well overnight at 4 °C. Plates were aspirated and blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature then washed in PBS containing 0.1% Tween 20 (PBST). Purified rabbit monoclonal antibodies diluted in PBST were added to the wells and incubated for 30 min at room temperature. This was followed by washing 6 times with PBST and incubation with Protein-A HRP conjugate at a 1:2000 dilution for a further 30 min. Plates were washed six times in PBST and incubated with tetramethylbenzidine (TMB) substrate for a further 15 min. The reaction was stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using at ELISA plate reader. ELISA with the mouse monoclonal antibodies was performed with supernatants from tissue culture run neat in the assay.

All of the antibodies bound to the recombinant P503S fragment, with the exception of the negative control SP2 supernatant. 20D4, JA1 and 1D12 bound strictly to peptide #2101 (SEQ ID NO: 504), which corresponds to amino acids 151-169 of SEQ ID NO: 114. 1C3 bound to peptide #2102 (SEQ ID NO: 505), which corresponds to amino acids 165-184 of SEQ ID NO: 114. 9C12 bound to peptide #2099 (SEQ ID NO: 522), which corresponds to amino acids 120-139 of SEQ ID NO: 114. The other antibodies bind to regions that were not examined in these studies.

Subsequent to epitope mapping, the antibodies were tested by FACS analysis on a cell line that stably expressed P503S to confirm that the antibodies bind to cell surface epitopes. Cells stably transfected with a control plasmid were employed as a negative control. Cells were stained live with no fixative. 0.5 ug of anti-P503S monoclonal antibody was added and cells were incubated on ice for 30 min before being washed twice and incubated with a FITC-labelled goat anti-rabbit or mouse secondary antibody for 20 min. After being washed twice, cells were analyzed with an Excalibur fluorescent activated cell sorter. The monoclonal antibodies 1C3, 1D12, 9C12, 20D4 and JA1, but not 8D3, were found to bind to a cell surface epitope of P503S.

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In order to determine which tissues express P503S, immunohistochemical analysis was performed, essentially as described above, on a panel of normal tissues (prostate, adrenal, breast, cervix, colon, duodenum, gall bladder, ileum, kidney, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis). HRP-labeled anti-mouse or anti-rabbit antibody followed by incubation with TMB was used to visualize P503S immunoreactivity. P503S was found to be highly expressed in prostate tissue, with lower levels of expression being observed in cervix, colon, ileum and kidney, and no expression being observed in adrenal, breast, duodenum, gall bladder, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis.

Western blot analysis was used to characterize anti-P503S monoclonal antibody specificity. SDS-PAGE was performed on recombinant (rec) P503S expressed in and purified from bacteria and on lysates from HEK293 cells transfected with full length P503S. Protein was transferred to nitrocellulose and then Western blotted with each of the anti-P503S monoclonal antibodies (20D4, JA1, 1D12, 6D12 and 9C12) at an antibody concentration of 1 ug/ml. Protein was detected using horse radish peroxidase (HRP) conjugated to either a goat anti-mouse monoclonal antibody or to protein A-sepharose. The monoclonal antibody 20D4 detected the appropriate molecular weight 14 kDa recombinant P503S (amino acids 113-241) and the 23.5 kDa species in the HEK293 cell lysates transfected with full length P503S. Other anti-P503S monoclonal antibodies displayed similar specificity by Western blot.

### D) PREPARATION AND CHARACTERIZATION OF ANTIBODIES AGAINST P703P

Rabbits were immunized with either a truncated (P703Ptr1; SEQ ID NO: 172) or full-length mature form (P703Pfl; SEQ ID NO: 523) of recombinant P703P protein was expressed in and purified from bacteria as described above. Affinity purified polyclonal antibody was generated using immunogen P703Pfl or P703Ptr1 attached to a solid support. Rabbit monoclonal antibodies were isolated using SLAM technology at Immgenics Pharmaceuticals. Table VII below lists both the polyclonal and monoclonal antibodies that were generated against P703P.

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Table VII

Antibody	Immunogen	Species/type
Aff. Purif. P703P (truncated); #2594	P703Ptrl	Rabbit polyclonal
Aff. Purif. P703P (full length); #9245	P703Pfl	Rabbit polyclonal
2D4	P703Ptrl	Rabbit monoclonal
8H2	P703Ptrl	Rabbit monoclonal
7H8	P703Ptrl	Rabbit monoclonal

The DNA sequences encoding the complementarity determining regions (CDRs) for the rabbit monoclonal antibodies 8H2, 7H8 and 2D4 were determined and are provided in SEQ ID NO: 506-508, respectively.

Epitope mapping studies were performed as described above. Monoclonal antibodies 2D4 and 7H8 were found to specifically bind to the peptides of SEQ ID NO: 509 (corresponding to amino acids 145-159 of SEQ ID NO: 172) and SEQ ID NO: 510 (corresponding to amino acids 11-25 of SEQ ID NO: 172), respectively. The polyclonal antibody 2594 was found to bind to the peptides of SEQ ID NO: 511-514, with the polyclonal antibody 9427 binding to the peptides of SEQ ID NO: 515-517.

The specificity of the anti-P703P antibodies was determined by Western blot analysis as follows. SDS-PAGE was performed on (1) bacterially expressed recombinant antigen; (2) lysates of HEK293 cells and Ltk-/- cells either untransfected or transfected with a plasmid expressing full length P703P; and (3) supernatant isolated from these cell cultures. Protein was transferred to nitrocellulose and then Western blotted using the anti-P703P polyclonal antibody #2594 at an antibody concentration of 1 ug/ml. Protein was detected using horse radish peroxidase (HRP) conjugated to an anti-rabbit antibody. A 35 kDa immunoreactive band could be observed with recombinant P703P. Recombinant P703P runs at a slightly higher molecular weight since it is epitope tagged. In lysates and supernatants from cells transfected with full length P703P, a 30 kDa band corresponding to P703P was observed. To assure specificity, lysates from HEK293 cells stably transfected

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with a control plasmid were also tested and were negative for P703P expression. Other anti-P703P antibodies showed similar results.

Immunohistochemical studies were performed as described above, using anti-P703P monoclonal antibody. P703P was found to be expressed at high levels in normal prostate and prostate tumor tissue but was not detectable in all other tissues tested (breast tumor, lung tumor and normal kidney).

### EXAMPLE 19

### CHARACTERIZATION OF CELL SURFACE EXPRESSION AND

### CHROMOSOME LOCALIZATION OF THE PROSTATE-SPECIFIC ANTIGEN P501S

This example describes studies demonstrating that the prostate-specific antigen P501S is expressed on the surface of cells, together with studies to determine the probable chromosomal location of P501S.

The protein P501S (SEQ ID NO: 113) is predicted to have 11 transmembrane domains. Based on the discovery that the epitope recognized by the anti-P501S monoclonal antibody 10E3-G4-D3 (described above in Example 17) is intracellular, it was predicted that following transmembrane determinants would allow the prediction of extracellular domains of P501S. Fig. 9 is a schematic representation of the P501S protein showing the predicted location of the transmembrane domains and the intracellular epitope described in Example 17. Underlined sequence represents the predicted transmembrane domains, bold sequence represents the predicted extracellular domains, and italicized sequence represents the predicted intracellular domains. Sequence that is both bold and underlined represents sequence employed to generate polyclonal rabbit serum. The location of the transmembrane domains was predicted using HHMTOP as described by Tusnady and Simon (Principles Governing Amino Acid Composition of Integral Membrane Proteins: Applications to Topology Prediction, *J. Mol. Biol. 283*:489-506, 1998).

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Based on Fig. 9, the P501S domain flanked by the transmembrane domains corresponding to amino acids 274-295 and 323-342 is predicted to be extracellular. The peptide of SEQ ID NO: 518 corresponds to amino acids 306-320 of P501S and lies in the predicted extracellular domain. The peptide of SEQ ID NO: 519, which is identical to the peptide of SEQ ID NO: 518 with the exception of the substitution of the histidine with an asparginine, was synthesized as described above. A Cys-Gly was added to the C-terminus of the peptide to facilitate conjugation to the carrier protein. Cleavage of the peptide from the solid support was carried out using the following cleavage mixture: trifluoroacetic acid:ethanediol:thioanisol:water:phenol (40:1:2:2:3). After cleaving for two hours, the peptide was precipitated in cold ether. The peptide pellet was then dissolved in 10% v/v acetic acid and lyophilized prior to purification by C18 reverse phase hplc. A gradient of 5-60% acetonitrile (containing 0.05% TFA) in water (containing 0.05% TFA) was used to elute the peptide. The purity of the peptide was verified by hplc and mass spectrometry, and was determined to be >95%. The purified peptide was used to generate rabbit polyclonal antisera as described above.

Surface expression of P501S was examined by FACS analysis. Cells were stained with the polyclonal anti-P501S peptide serum at 10 µg/ml, washed, incubated with a secondary FITC-conjugated goat anti-rabbit Ig antibody (ICN), washed and analyzed for FITC fluorescence using an Excalibur fluorescence activated cell sorter. For FACS analysis of transduced cells, B-LCL were retrovirally transduced with P501S. To demonstrate specificity in these assays, B-LCL transduced with an irrelevant antigen (P703P) or nontransduced were stained in parallel. For FACS analysis of prostate tumor cell lines, Lncap, PC-3 and DU-145 were utilized. Prostate tumor cell lines were dissociated from tissue culture plates using cell dissociation medium and stained as above. All samples were treated with propidium iodide (PI) prior to FACS analysis, and data was obtained from PI-excluding (*i.e.*, intact and non-permeabilized) cells. The rabbit polyclonal serum generated against the peptide of SEQ ID NO: 519 was shown to specifically recognize the surface of cells transduced to express P501S, demonstrating that the epitope recognized by the polyclonal serum is extracellular.

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To determine biochemically if P501S is expressed on the cell surface, peripheral membranes from Lncap cells were isolated and subjected to Western blot analysis. Specifically, Lncap cells were lysed using a dounce homogenizer in 5 ml of homogenization buffer (250 mM sucrose, 10 mM HEPES, 1mM EDTA, pH 8.0, 1 complete protease inhibitor tablet (Boehringer Mannheim)). Lysate samples were spun at 1000 g for 5 min at 4 °C. The supernatant was then spun at 8000g for 10 min at 4 °C. Supernatant from the 8000g spin was recovered and subjected to a 100,000g spin for 30 min at 4 °C to recover peripheral membrane. Samples were then separated by SDS-PAGE and Western blotted with the mouse monoclonal antibody 10E3-G4-D3 (described above in Example 17) using conditions described above. Recombinant purified P501S, as well as HEK293 cells transfected with and over-expressing P501S were included as positive controls for P501S detection. LCL cell lysate was included as a negative control. P501S could be detected in Lncap total cell lysate, the 8000g (internal membrane) fraction and also in the 100,000g (plasma membrane) fraction. These results indicate that P501S is expressed at, and localizes to, the peripheral membrane.

To demonstrate that the rabbit polyclonal antiserum generated to the peptide of SEQ ID NO: 519 specifically recognizes this peptide as well as the corresponding native peptide of SEQ ID NO: 518, ELISA analyses were performed. For these analyses, flat-bottomed 96 well microtiter plates were coated with either the peptide of SEQ ID NO: 519, the longer peptide of SEQ ID NO: 520 that spans the entire predicted extracellular domain, the peptide of SEQ ID NO: 521 which represents the epitope recognized by the P501S-specific antibody 10E3-G4-D3, or a P501S fragment (corresponding to amino acids 355-526 of SEQ ID NO: 113) that does not include the immunizing peptide sequence, at 1 μg/ml for 2 hours at 37 °C. Wells were aspirated, blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature and subsequently washed in PBS containing 0.1% Tween 20 (PBST). Purified anti-P501S polyclonal rabbit serum was added at 2 fold dilutions (1000 ng - 125 ng) in PBST and incubated for 30 min at room temperature. This was followed by washing 6 times with PBST and incubating with HRP-conjugated goat anti-rabbit IgG (H+L) Affinipure F(ab') fragment at 1:20000 for 30 min.

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Plates were then washed and incubated for 15 min in tetramethyl benzidine. Reactions were stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using an ELISA plate reader. As shown in Fig. 11, the anti-P501S polyclonal rabbit serum specifically recognized the peptide of SEQ ID NO: 519 used in the immunization as well as the longer peptide of SEQ ID NO: 520, but did not recognize the irrelevant P501S-derived peptides and fragments.

In further studies, rabbits were immunized with peptides derived from the P501S sequence and predicted to be either extracellular or intracellular, as shown in Fig. 9. Polyclonal rabbit sera were isolated and polyclonal antibodies in the serum were purified, as described above. To determine specific reactivity with P501S, FACS analysis was employed, utilizing either B-LCL transduced with P501S or the irrelevant antigen P703P, of B-LCL infected with vaccinia virus-expressing P501S. For surface expression, dead and non-intact cells were excluded from the analysis as described above. For intracellular staining, cells were fixed and permeabilized as described above. Rabbit polyclonal serum generated against the peptide of SEQ ID NO: 548, which corresponds to amino acids 181-198 of P501S, was found to recognize a surface epitope of P501S. Rabbit polyclonal serum generated against the peptide SEQ ID NO: 551, which corresponds to amino acids 543-553 of P501S, was found to recognize an epitope that was either potentially extracellular or intracellular since in different experiments intact or permeabilized cells were recognized by the polyclonal sera. Based on similar deductive reasoning, the sequences of SEQ ID NO: 541-547, 549 and 550, which correspond to amino acids 109-122, 539-553, 509-520, 37-54, 342-359, 295-323, 217-274, 143-160 and 75-88, respectively, of P501S, can be considered to be potential surface epitopes of P501S recognized by antibodies.

The chromosomal location of P501S was determined using the GeneBridge 4 Radiation Hybrid panel (Research Genetics). The PCR primers of SEQ ID NO: 528 and 529 were employed in PCR with DNA pools from the hybrid panel according to the manufacturer's directions. After 38 cycles of amplification, the reaction products were separated on a 1.2% agarose gel, and the results were analyzed through the Whitehead

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Institute/MIT Center for Genome Research web server (http://www-genome.wi.mit.edu/cgi-bin/contig/rhmapper.pl) to determine the probable chromosomal location. Using this approach, P501S was mapped to the long arm of chromosome 1 at WI-9641 between q32 and q42. This region of chromosome 1 has been linked to prostate cancer susceptibility in hereditary prostate cancer (Smith *et al. Science 274*:1371-1374, 1996 and Berthon *et al. Am. J. Hum. Genet. 62*:1416-1424, 1998). These results suggest that P501S may play a role in prostate cancer malignancy.

### **EXAMPLE 20**

REGULATION OF EXPRESSION OF THE PROSTATE-SPECIFIC ANTIGEN P501S

Steroid (androgen) hormone modulation is a common treatment modality in prostate cancer. The expression of a number of prostate tissue-specific antigens have previously been demonstrated to respond to androgen. The responsiveness of the prostate-specific antigen P501S to androgen treatment was examined in a tissue culture system as follows.

Cells from the prostate tumor cell line LNCaP were plated at 1.5 x 10<sup>6</sup> cells/T75 flask (for RNA isolation) or 3 x 10<sup>5</sup> cells/well of a 6-well plate (for FACS analysis) and grown overnight in RPMI 1640 media containing 10% charcoal-stripped fetal calf serum (BRL Life Technologies, Gaithersburg, MD). Cell culture was continued for an additional 72 hours in RPMI 1640 media containing 10% charcoal-stripped fetal calf serum, with 1 nM of the synthetic androgen Methyltrienolone (R1881; New England Nuclear) added at various time points. Cells were then harvested for RNA isolation and FACS analysis at 0, 1, 2, 4, 8, 16, 24, 28 and 72-hours post androgen addition. FACS analysis was performed using the anti-P501S antibody 10E3-G4-D3 and permeabilized cells.

For Northern analysis, 5-10 micrograms of total RNA was run on a formaldehyde denaturing gel, transferred to Hybond-N nylon membrane (Amersham Pharmacia Biotech, Piscataway, NJ), cross-linked and stained with methylene blue. The

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filter was then prehybridized with Church's Buffer (250 mM Na<sub>2</sub>HPO<sub>4</sub>, 70 mM H<sub>3</sub>PO<sub>4</sub>, 1 mM EDTA, 1% SDS, 1% BSA in pH 7.2) at 65 °C for 1 hour. P501S DNA was labeled with 32P using High Prime random-primed DNA labeling kit (Boehringer Mannheim). Unincorporated label was removed using MicroSpin S300-HR columns (Amersham Pharmacia Biotech). The RNA filter was then hybridized with fresh Church's Buffer containing labeled cDNA overnight, washed with 1X SCP (0.1 M NaCl, 0.03 M Na<sub>2</sub>HPO<sub>4</sub>.7H<sub>2</sub>O, 0.001 M Na<sub>2</sub>EDTA), 1% sarkosyl (n-lauroylsarcosine) and exposed to X-ray film.

Using both FACS and Northern analysis, P501S message and protein levels
were found in increase in response to androgen treatment.

### EXAMPLE 20

# PREPARATION OF FUSION PROTEINS OF PROSTATE-SPECIFIC ANTIGENS

The example describes the preparation of a fusion protein of the prostate-specific antigen P703P and a truncated form of the known prostate antigen PSA. The truncated form of PSA has a 21 amino acid deletion around the active serine site. The expression construct for the fusion protein also has a restriction site at 3' end, immediately prior to the termination codon, to aid in adding cDNA for additional antigens.

The full-length cDNA for PSA was obtained by RT-PCR from a pool of RNA from human prostate tumor tissues using the primers of SEQ ID NO: 607 and 608, and cloned in the vector pCR-Blunt II-TOPO. The resulting cDNA was employed as a template to make two different fragments of PSA by PCR with two sets of primers (SEQ ID NO: 609 and 610; and SEQ ID NO: 611 and 612). The PCR products having the expected size were used as templates to make truncated forms of PSA by PCR with the primers of SEQ ID NO: 611 and 613, which generated PSA (delta 208-218 in amino acids). The cDNA for the mature form of P703P with a 6X histidine tag at the 5' end, was prepared by PCR with P703P and the primers of SEQ ID NO: 614 and 615. The cDNA for the fusion of P703P with the truncated form of PSA (referred to as FOPP) was then

obtained by PCR using the modified P703P cDNA and the truncated form of PSA cDNA as templates and the primers of SEQ ID NO: 614 and 615. The FOPP cDNA was cloned into the NdeI site and XhoI site of the expression vector pCRX1, and confirmed by DNA sequencing. The determined cDNA sequence for the fusion construct FOPP is provided in SEQ ID NO: 616, with the amino acid sequence being provided in SEQ ID NO: 617.

# **EXAMPLE 21**

# REAL-TIME PCR CHARACTERIZATION OF THE PROSTATE-SPECIFIC ANTIGEN P501S IN PERIPHERAL BLOOD OF PROSTATE CANCER PATIENTS

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Circulating epithelial cells were isolated from fresh blood of normal individuals and metastatic prostate cancer patients, mRNA isolated and cDNA prepared using real-time PCR procedures. Real-time PCR was performed with the Taqman<sup>TM</sup> procedure using both gene specific primers and probes to determine the levels of gene expression.

Epithelial cells were enriched from blood samples using an immunomagnetic bead separation method (Dynal A.S., Oslo, Norway). Isolated cells were lysed and the magnetic beads removed. The lysate was then processed for poly A+ mRNA isolation using magnetic beads coated with Oligo(dT)25. After washing the beads in buffer, bead/poly A+ RNA samples were suspended in 10 mM Tris HCl pH 8.0 and subjected to reversed transcription. The resulting cDNA was subjected to real-time PCR using gene specific primers. Beta-actin content was also determined and used for normalization. Samples with P501S copies greater than the mean of the normal samples + 3 standard deviations were considered positive. Real time PCR on blood samples was performed using the Taqman<sup>TM</sup> procedure but extending to 50 cycles using forward and reverse primers and probes specific for P501S. Of the eight samples tested, 6 were positive for P501S and β-actin signal. The remaining 2 samples had no detectable β-actin or P501S. No P501S signal was observed in the four normal blood samples tested.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the present invention is not limited except as by the appended claims.

### **CLAIMS**

What is claimed:

- 1. An isolated polypeptide, comprising at least an immunogenic portion of a prostate-specific protein, wherein the protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (a) sequences recited in SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772 and 779;
- (b) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772 and 779 under moderately stringent conditions; and
  - (c) complements of sequences of (a) or (b).
- 2. An isolated polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434,

435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772 and 779, or a complement of any of the foregoing polynucleotide sequences.

- 3. An isolated polypeptide comprising a sequence recited in any one of SEQ ID NO: 108, 112, 113, 114, 172, 176, 178, 327, 329, 331, 338, 339, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 706-708, 780, 781, 810, 811 and 814.
- 4. An isolated polynucleotide encoding at least 15 amino acid residues of a prostate-specific protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772 and 779, or a complement of any of the foregoing sequences.
- 5. An isolated polynucleotide encoding a prostate-specific protein, or a variant thereof, wherein the protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-

461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772 and 779, or a complement of any of the foregoing sequences.

- 6. An isolated polynucleotide, comprising a sequence recited in any one of SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772 and 779.
- 7. An isolated polynucleotide, comprising a sequence that hybridizes to a sequence recited in any one of SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772 and 779 under moderately stringent conditions.
- 8. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 4-7.
- 9. An expression vector, comprising a polynucleotide according to any one of claims 4-8.
- 10. A host cell transformed or transfected with an expression vector according to claim 9.

- 11. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a prostate-specific protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772 and 779, or a complement of any of the foregoing polynucleotide sequences.
  - 12. A fusion protein, comprising at least one polypeptide according to claim 1.
- 13. A fusion protein according to claim 12, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.
- 14. A fusion protein according to claim 12, wherein the fusion protein comprises a T helper epitope that is not present within the polypeptide of claim 1.
- 15. A fusion protein according to claim 12, wherein the fusion protein comprises an affinity tag.
- 16. An isolated polynucleotide encoding a fusion protein according to claim 12.
- 17. A pharmaceutical composition, comprising a physiologically acceptable carrier and at least one component selected from the group consisting of:
  - (a) a polypeptide according to claim 1;

- (b) a polynucleotide according to claim 4;
- (c) an antibody according to claim 11;
- (d) a fusion protein according to claim 12; and
- (e) a polynucleotide according to claim 16.
- 18. An immunogenic composition comprising an immunostimulant and at least one component selected from the group consisting of:
  - (a) a polypeptide according to claim 1;
  - (b) a polynucleotide according to claim 4;
  - (c) an antibody according to claim 11;
  - (d) a fusion protein according to claim 12; and
  - (e) a polynucleotide according to claim 16.
- 19. An immunogenic composition according to claim 18, wherein the immunostimulant is an adjuvant.
- 20. An immunogenic composition according to claim 18, wherein the immunostimulant induces a predominantly Type I response.
- 21. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 17.
- 22. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an immunogenic composition according to claim 18.

- 23. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.
- 24. A pharmaceutical composition according to claim 23, wherein the antigen presenting cell is a dendritic cell or a macrophage.
- 25. An immunogenic composition comprising an antigen-presenting cell that expresses a polypeptide comprising at least an immunogenic portion of a prostate-specific protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (a) sequences recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789;
- (b) sequences that hybridize to a sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789 under moderately stringent conditions; and
  - (c) complements of sequences of (i) or (ii); in combination with an immunostimulant.
- 26. An immunogenic composition according to claim 25, wherein the immunostimulant is an adjuvant.
- 27. An immunogenic composition according to claim 25, wherein the immunostimulant induces a predominantly Type I response.
- 28. An immunogenic composition according to claim 25, wherein the antigenpresenting cell is a dendritic cell.

- 29. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide comprising at least an immunogenic portion of a prostate-specific protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (a) sequences recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789;
- (b) sequences that hybridize to a sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789 under moderately stringent conditions; and
- (c) complements of sequences of (i) or (ii)encoded by a polynucleotide recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789;

and thereby inhibiting the development of a cancer in the patient.

- 30. A method according to claim 29, wherein the antigen-presenting cell is a dendritic cell.
- 31. A method according to any one of claims 21, 22 and 29, wherein the cancer is prostate cancer.
- 32. A method for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a prostate-specific protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

- (i) polynucleotides recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789; and
  - (ii) complements of the foregoing polynucleotides;

wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the antigen from the sample.

- 33. A method according to claim 32, wherein the biological sample is blood or a fraction thereof.
- 34. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 32.
- 35. A method for stimulating and/or expanding T cells specific for a prostate-specific protein, comprising contacting T cells with at least one component selected from the group consisting of:
- (a) polypeptides comprising at least an immunogenic portion of a prostatespecific protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (i) sequences recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789;
- (ii) sequences that hybridize to a sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789 under moderately stringent conditions; and
  - (iii) complements of sequences of (i) or (ii);

- (b) polynucleotides encoding a polypeptide of (a); and
- (c) antigen presenting cells that express a polypeptide of (a);

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

- 36. An isolated T cell population, comprising T cells prepared according to the method of claim 35.
- 37. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population according to claim 36.
- 38. A method for inhibiting the development of a cancer in a patient, comprising the steps of:
- (a) incubating CD4<sup>+</sup> and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:
- (i) polypeptides comprising at least an immunogenic portion of a prostate-specific protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (1) sequences recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789;
- (2) sequences that hybridize to a sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789 under moderately stringent conditions; and
  - (3) complements of sequences of (1) or (2);
  - (ii) polynucleotides encoding a polypeptide of (i); and
  - (iii) antigen presenting cells that expresses a polypeptide of (i);

such that T cells proliferate; and

- (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.
- 39. A method for inhibiting the development of a cancer in a patient, comprising the steps of:
- (a) incubating CD4<sup>+</sup> and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:
- (i) polypeptides comprising at least an immunogenic portion of a prostate-specific protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (1) sequences recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789;
- (2) sequences that hybridize to a sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789 under moderately stringent conditions; and
  - (3) complements of sequences of (1) or (2);
  - (ii) polynucleotides encoding a polypeptide of (i); and
  - (iii) antigen presenting cells that express a polypeptide of (i); such that T cells proliferate;
  - (b) cloning at least one proliferated cell to provide cloned T cells; and
- (c) administering to the patient an effective amount of the cloned T cells, and thereby inhibiting the development of a cancer in the patient.
- 40. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

- (a) contacting a biological sample obtained from a patient with a binding agent that binds to a prostate-specific protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789 or a complement of any of the foregoing polynucleotide sequences;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.
  - 41. A method according to claim 40, wherein the binding agent is an antibody.
- 42. A method according to claim 43, wherein the antibody is a monoclonal antibody.
  - 43. A method according to claim 40, wherein the cancer is prostate cancer.
- 44. A method for monitoring the progression of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a prostate-specific protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789 or a complement of any of the foregoing polynucleotide sequences;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent;

- (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and
- (d) comparing the amount of polypeptide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.
  - 45. A method according to claim 44, wherein the binding agent is an antibody.
- 46. A method according to claim 45, wherein the antibody is a monoclonal antibody.
  - 47. A method according to claim 44, wherein the cancer is a prostate cancer.
- 48. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate-specific protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789, or a complement of any of the foregoing polynucleotide sequences;
- (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and
- (c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.
- 49. A method according to claim 48, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

- 50. A method according to claim 48, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.
- 51. A method for monitoring the progression of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate-specific protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777 and 789, or a complement of any of the foregoing polynucleotide sequences;
- (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide;
- (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and
- (d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.
- 52. A method according to claim 51, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.
- 53. A method according to claim 51, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.
  - 54. A diagnostic kit, comprising:
  - (a) one or more antibodies according to claim 11; and
  - (b) a detection reagent comprising a reporter group.

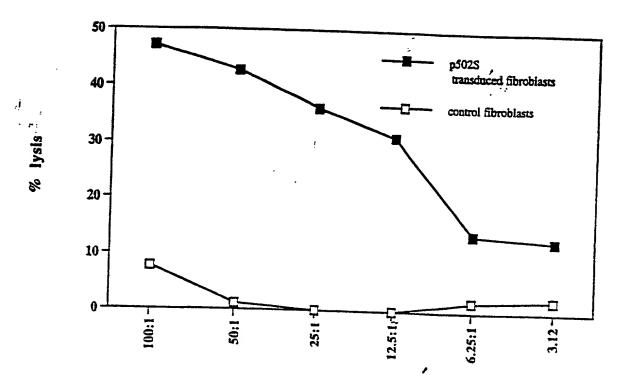
- 55. A kit according to claim 54, wherein the antibodies are immobilized on a solid support.
- 56. A kit according to claim 54, wherein the detection reagent comprises an anti-immunoglobulin, protein G, protein A or lectin.
- 57. A kit according to claim 54, wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.
- 58. An oligonucleotide comprising 10 to 40 contiguous nucleotides that hybridize under moderately stringent conditions to a polynucleotide that encodes a prostate-specific protein, wherein the protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772 and 779, or a complement of any of the foregoing polynucleotides.
- 59. A oligonucleotide according to claim 58, wherein the oligonucleotide comprises 10-40 contiguous nucleotides recited in any one of SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772 and 779.

- 60. A diagnostic kit, comprising:
- (a) an oligonucleotide according to claim 59; and
- (b) a diagnostic reagent for use in a polymerase chain reaction or hybridization assay.

# COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF PROSTATE CANCER

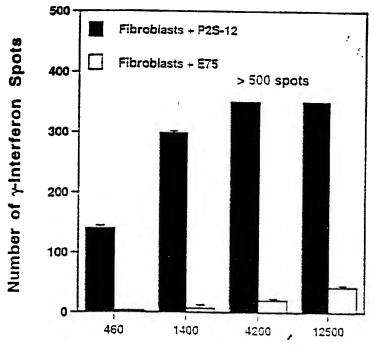
# ABSTRACT OF THE DISCLOSURE

Compositions and methods for the therapy and diagnosis of cancer, such as prostate cancer, are disclosed. Compositions may comprise one or more prostate-specific proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a prostate-specific protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as prostate cancer. Diagnostic methods based on detecting a prostate-specific protein, or mRNA encoding such a protein, in a sample are also provided.



Effector: Target Ratio

FIG. 1



Number of Responders

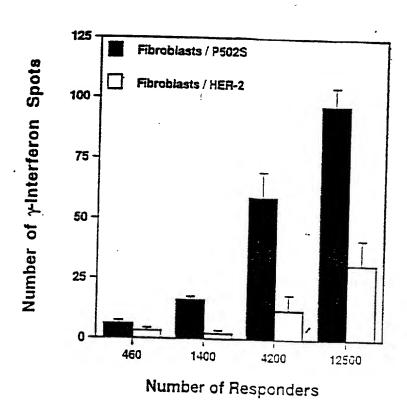


FIG. 2B



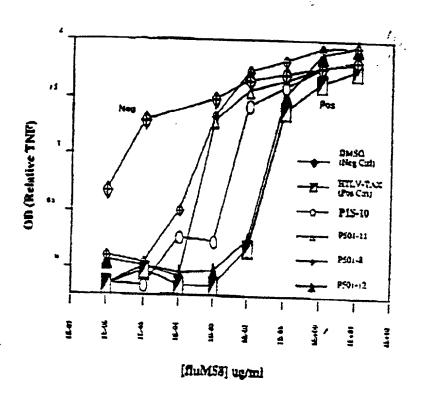


Figure 3

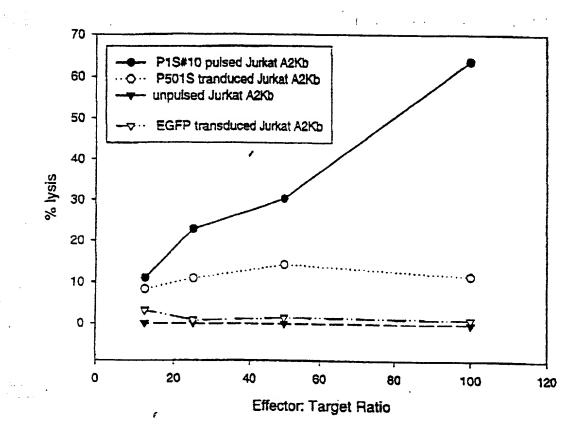


Figure 4

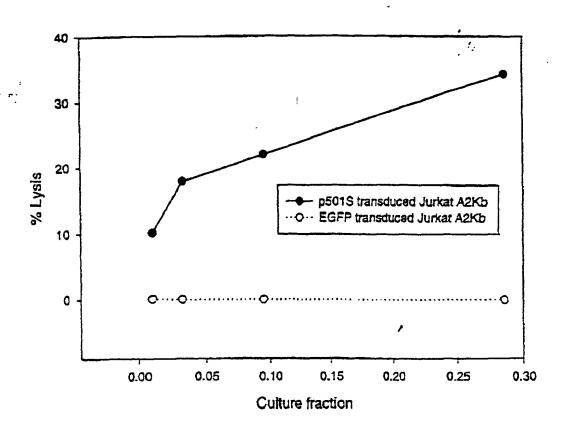
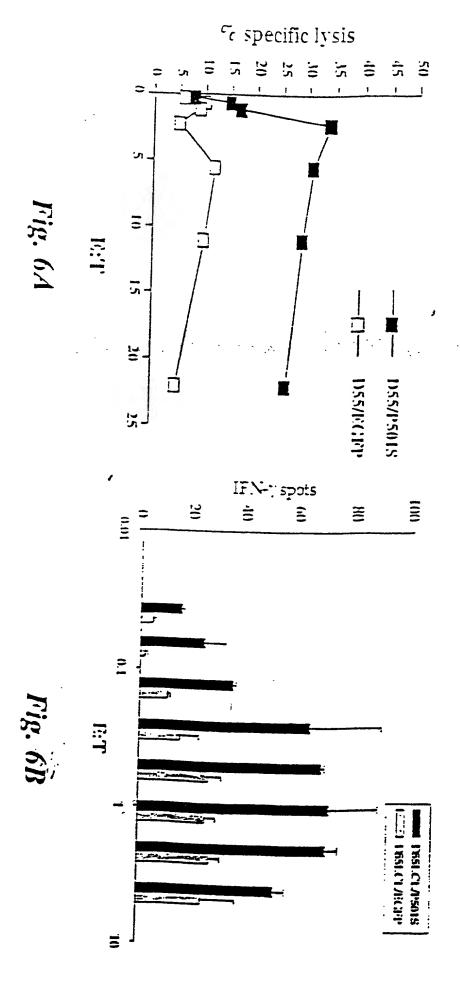
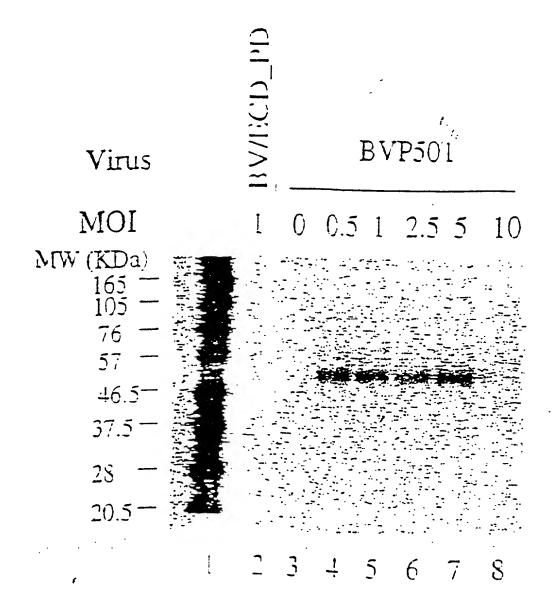


Figure 5



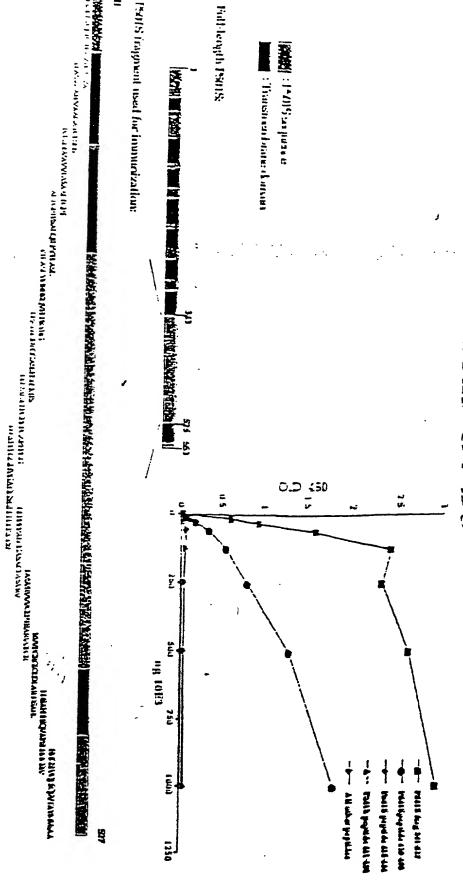
# Expression of P501S by the Bandovirus Expression System



control virus BV/ECD\_PD PAGE under the reducing of mencelonal anabody agains? To protein molecular weight mile

0.6 million high bis a bowell place were infected with an unrelated without virus (lane 3), or with recombinant baculovirus for P501 at differe (% 1% lane 4 - %). Cell lysates, were run on SDSone analyzed by Western bloc with a > 030.8-10E3-0403 Land List the blodhylated distate.

# Figure 8. Mapping of the epitope recognized by 10E3-G4-D3



# transmembrane, cytoplasmic, and extracellular regions Figure 1. Schematic of P501S with predicted

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FALLSDLERDPDIGRO AYSYYADABISLOOCI ONLI PAL DWDTSALAPYLOTOIG

CLEGILITERICYANTEN AFFAALGPTEPAEGESAPSESPIET PERAKAFRAIAPRE

HOLGGRAFFRER LIPVAFILGSPOMMI MITERI FYTDF YGEGLYOGYFRAIPGILARRIYDEGYH

MÜBLÖLLTQCARLYFRLYM *drivqregtravilas* yaaffyaagat**clshsyayyta saa** 

LTGETESA<u>loil</u>eytil**as**ly hrekqvetekyroptggassedstaitsetegpkpgapfpnghygagggl

LPPPPALCOASACDYSVRVVORPTEARVVPGRG | ICLDIANIDSAULSQYAPSLE | MG8IVQLSQ8

YTAYMVSAAGILGILYAIYFAT QVVFDKSDLAKYSA

Indic sequence: Predicted intracellular domain. Sequence in bold/anderlined: used to generale polyclonal rabbit serum Underlined sequence: Predicted transmembrane domain; Bold sequence: Predicted extracellular domain;

Cloverning Amino Acid Composition of Integral Membrane Proteins: Applications to topology Prediction. J.Mol Riol. 283, Localization of domains predicted using HMMTOP (G.R. Tusnady and I. Simon (1998) Principles

Genomic Map of (5) Corixa Candidate Genes

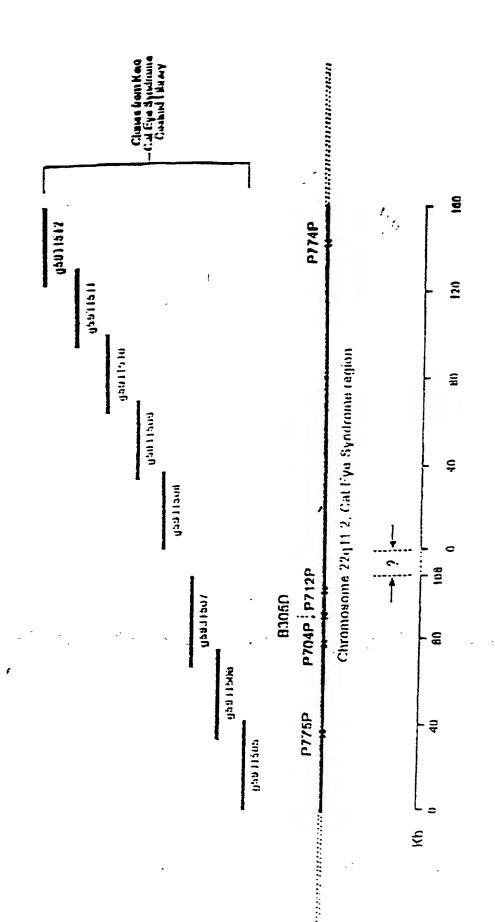
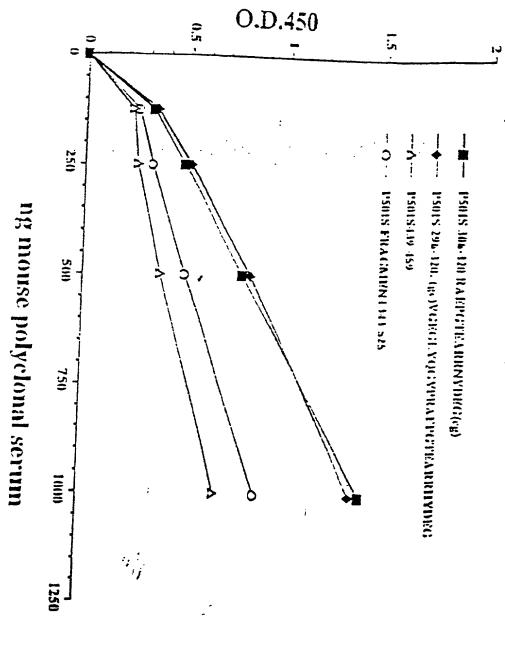


Fig. 10

# FIGURE 4. Elisa assay of rabbit polyclonal antibody specificity



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10
                               30
                                         40
                     20
                                                  50
                                                            60
                                                                      70
  GTCACTTAGGAAAAGGTGTCCTTTCGGGCAGCCGGGCTCAGCATGAGGAACAGAAGGAATGACACTCTGG 70
  ACAGCACCCGGACCCTGTACTCCAGCGCGTCTCGGAGCACAGACTTGTCTTACACTGAAAGCGACTTGGT 140
  GAATTTTATTCAAGCAAATTTTAAGAAACGAGAATGTGTCTTCTTTACCAAAGATTCCAAGGCCACGGAG 210
  AATGTGTGCAAGTGTGGCTATGCCCAGAGCCAGCACATGGAAGGCACCCAGATCAACCAAAGTGAGAAAT 280
  GGAACTACAAGAACACACCAAGGAATTTCCTACCGACGCCTTTGGGGATATTCAGTTTGAGACACTGGG 350
          360
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Fig. 12A(3)

1-2

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## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants

Jiangchun Xu et al.

Filed

: June 13, 2000

For

COMPOSITIONS AND METHODS FOR THERAPY AND

DIAGNOSIS OF PROSTATE CANCER

Docket No.

210121.42715C15

Date

June 13, 2000

Box Patent Application Assistant Commissioner for Patents Washington, D.C. 20231

## **DECLARATION**

Sir:

I, Monica Steinborn, in accordance with 37 C.F.R. § 1.821(f) do hereby declare that, to the best of my knowledge, the content of the paper entitled "Sequence Listing" and the computer readable copy contained within the floppy disk are the same.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated this 13th day of June, 2000.

1 Steinburn

Monica Steinborn Legal Assistant

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Wpn/210121 - Corixa/42715c15/42715c15dec.doc

## SEQUENCE LISTING

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<110> Xu, Jiangchun
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            Day, Craig H.
            Vedvick, Thomas S.
            Carter, Darrick
            Li, Samuel
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agateetgee etacacaetg geeteeetet accaceggga gaageaggtg tteetgeeca
                                                                       180
aataccgagg ggacactgga ggtgctagca gtgaggacag cctgatgacc agcttcctgc
                                                                       240
caggccctaa gcctggagct cccttcccta atggacacgt gggtgctgga ggcagtggcc
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tgeteccace tecaceegeg etetgegggg cetetgeetg tgatgtetee gtacgtgtgg
                                                                       360
tggtgggtga gcccaccgan gccagggtgg ttccgggccg gggcatctgc ctggacctcg
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ccatectgga tagtgettee tgetgteeca ngtggeecea tecetgttta tqqqetecat
                                                                       480
tgtccagctc agccagtctg tcactgccta tatggtgtct gccgcaggcc tgggtctggt
                                                                       540
cccatttact ttgctacaca ggtantattt gacaagaacg anttggccaa atactcaqcq
                                                                       600
ttaaaaaatt ccagcaacat tgggggtgga aggcctgcct cactgggtcc aactccccgc
                                                                       660
tectgttaac cecatgggge tgeeggettg geegecaatt tetgttgetg ceaaantnat
                                                                       720
gtggctctct gctgccacct gttgctggct gaagtgcnta cngcncanct nggggggtng
                                                                       780
ggngttccc
                                                                       789
      <210> 11
      <211> 772
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(772)
      <223> n = A, T, C or G
      <400> 11
cccaccctac ccaaatatta gacaccaaca cagaaaagct agcaatggat tcccttctac
                                                                        60
tttgttaaat aaataagtta aatatttaaa tgcctgtgtc tctgtgatgg caacagaagg
                                                                       120
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accaacaggc cacatcctga taaaaggtaa gaggggggtg gatcagcaaa aagacagtgc

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tgtgggctga ggggacctgg ttcttgtgtg ttgcccctca ggactcttcc cctacaaata
                                                                        240
actiticatat giticaaatic catggaggag tgititicatic tagaaactic catgcaagag
                                                                        300
ctacattaaa cgaagctgca ggttaagggg cttanagatg ggaaaccagg tgactgagtt
                                                                        360
tattcagctc ccaaaaaccc ttctctaggt gtgtctcaac taggaggcta gctgttaacc
                                                                        420
ctgagcctgg gtaatccacc tgcagagtcc ccgcattcca gtgcatggaa cccttctggc
                                                                        480
ctccctgtat aagtccagac tgaaaccccc ttggaaggnc tccagtcagg cagccctana
                                                                        540
aactggggaa aaaagaaaag gacgccccan cccccagctg tgcanctacg cacctcaaca
                                                                        600
gcacagggtg gcagcaaaaa aaccacttta ctttggcaca aacaaaaact ngggggggca
                                                                        660
accceggeac ceenangggg gttaacagga anengggnaa entggaacce aattnaggea
                                                                        720
ggcccnccac cccnaatntt gctgggaaat ttttcctccc ctaaattntt tc
                                                                        772
      <210> 12
      <211> 751
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(751)
      <223> n = A, T, C \text{ or } G
      <400> 12
gccccaattc cagctgccac accacccacg gtgactgcat tagttcggat gtcatacaaa
                                                                         60
agetgattga ageaaceete taetttttgg tegtgageet tttgettggt geaggtttea
                                                                        120
ttggctgtgt tggtgacgtt gtcattgcaa cagaatgggg gaaaggcact gttctctttg
                                                                        180
aagtanggtg agtcctcaaa atccgtatag ttggtgaagc cacagcactt gagccctttc
                                                                        240
atggtggtgt tecacacttg agtgaagtet teetgggaae cataatettt ettgatggca
                                                                        300
ggcactacca gcaacgtcag ggaagtgctc agccattgtg gtgtacacca aggcgaccac
                                                                        360
agcagctgcn acctcagcaa tgaagatgan gaggangatg aagaagaacg tcncgagggc
                                                                        420
acacttgctc tcagtcttan caccatanca gcccntgaaa accaananca aagaccacna
                                                                        480
cnccggctgc gatgaagaaa tnaccccncg ttgacaaact tgcatggcac tggganccac
                                                                        540
agtggcccna aaaatettca aaaaggatge eecatenatt gaeeeecaa atgeeeactg
                                                                        600
ccaacagggg ctgccccacn cncnnaacga tganccnatt gnacaagatc tncntggtct
                                                                        660
tnatnaacht gaaccetgen tngtggetee tgtteaggne ennggeetga ettetnaann
                                                                        720
aangaacton gaagnoocca enggananne g
                                                                        751
      <210> 13
      <211> 729
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(729)
      \langle 223 \rangle n = A,T,C or G
      <400> 13
gagccaggcg tecetetgce tgcccactca gtggcaacac cegggagetg ttttgteett
                                                                         60
tgtggancct cagcagtncc ctctttcaga actcantgcc aaganccctg aacaggagcc
                                                                        120
accatgoagt gottcagott cattaagaco atgatgatoo tottcaattt gotcatottt
                                                                        180
```

ctgtgtggtg cagccctgtt ggcagtgggc atctgggtgt caatcgatgg ggcatccttt

```
ctgaagatct tcgggccact gtcgtccagt gccatgcagt ttgtcaacgt gggctacttc
                                                                        300
ctcatcgcag ccggcgttgt ggtcttagct ctaggtttcc tgggctgcta tggtgctaag
                                                                        360
actgagagca agtgtgccct cgtgacgttc ttcttcatcc tcctcctcat cttcattgct
                                                                        420
gaggttgcaa tgctgtggtc gccttggtgt acaccacaat ggctgagcac ttcctgacgt
                                                                        480
tgctggtaat gcctgccatc aanaaaagat tatgggttcc caggaanact tcactcaagt
                                                                        540
gttggaacac caccatgaaa gggctcaagt gctgtggctt cnnccaacta tacggatttt
                                                                        600
gaagantcac ctacttcaaa gaaaanagtg cctttccccc atttctgttg caattgacaa
                                                                       660
acgtccccaa cacagccaat tgaaaacctg cacccaaccc aaangggtcc ccaaccanaa
                                                                       720
attnaaggg
                                                                       729
      <210> 14
      <211> 816
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(816)
      <223> n = A, T, C \text{ or } G
      <400> 14
tgctcttcct caaagttgtt cttgttgcca taacaaccac cataggtaaa gcgggcqcaq
                                                                        60
tgttcgctga aggggttgta gtaccagcgc gggatgctct ccttgcagag tcctgtgtct
                                                                       120
ggcaggtcca cgcagtgccc tttgtcactg gggaaatgga tgcgctggag ctcgtcaaag
                                                                       180
ccactcgtgt attittcaca ggcagcctcg tccgacgcgt cggggcagtt gggggtgtct
                                                                       240
tcacactcca ggaaactgtc natgcagcag ccattgctgc agcggaactg ggtgggctga
                                                                       300
cangtgccag agcacactgg atggcgcctt tccatgnnan gggccctgng ggaaagtccc
                                                                       360
tganccccan anctgeetet caaangeece acettgeaca eecegacagg etagaatgga
                                                                       420
atcttcttcc cgaaaggtag ttnttcttgt tgcccaancc anccccntaa acaaactctt
                                                                       480
gcanatetge teegnggggg tentantace anegtgggaa aagaacecea ggengegaae
                                                                       540
caancttgtt tggatncgaa gcnataatct nctnttctgc ttggtggaca gcaccantna
                                                                       600
ctgtnnanct ttagnccntg gtcctcntgg gttgnncttg aacctaatcn ccnntcaact
                                                                       660
gggacaaggt aantngccnt cctttnaatt cccnancntn ccccctggtt tggggttttn
                                                                       720
cncnctccta ccccagaaan nccgtgttcc cccccaacta ggggccnaaa ccnnttnttc
                                                                       780
cacaaccctn ccccacccac gggttcngnt ggttng
                                                                       816
      <210> 15
      <211> 783
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(783)
      <223> n = A,T,C or G
      <400> 15
ccaaggeetg ggeaggeata nacttgaagg tacaacccca ggaacccctg gtgctgaagg
                                                                        60
atgtggaaaa cacagattgg cgcctactgc ggggtgacac ggatgtcagg gtagagagga
                                                                       120
aagacccaaa ccaggtggaa ctgtggggac tcaaggaang cacctacctg ttccagctga
                                                                       180
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cagtgactag ctcagaccac ccagaggaca cggccaacgt cacagtcact gtgctgtcca

```
ccaagcagac agaagactac tgcctcgcat ccaacaangt gggtcgctgc cggggctctt
                                                                        300
teccaegetg gtaetatgae eecaeggage agatetgeaa gagtttegtt tatggagget
                                                                        360
gcttgggcaa caagaacaac taccttcggg aagaagagtg cattctancc tgtcngggtg
                                                                        420
tgcaaggtgg gcctttgana ngcanctctg gggctcangc gactttcccc cagggcccct
                                                                        480
ccatggaaag gcgccatcca ntgttctctg gcacctgtca gcccacccag ttccgctgca
                                                                        540
ncaatggctg ctgcatcnac antttcctng aattgtgaca acacccccca ntgcccccaa
                                                                        600
ccctcccaac aaagcttccc tgttnaaaaa tacnccantt ggcttttnac aaacncccgg
                                                                        660
enceteentt tteecenntn aacaaaggge netngenttt gaactgeeen aaccenggaa
                                                                        720
tetneenngg aaaaantnee eeceetggtt eetnnaanee eeteenenaa anetneeeee
                                                                        780
                                                                        783
      <210> 16
      <211> 801
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(801)
      \langle 223 \rangle n = A,T,C or G
      <400> 16
gccccaatte cagetgccac accacccacg gtgactgcat tagttcggat gtcatacaaa
                                                                         60
agctgattga agcaaccete tactttttgg tegtgageet tttgettggt geaggtttea
                                                                       120
ttggctgtgt tggtgacgtt gtcattgcaa cagaatgggg gaaaggcact gttctctttg
                                                                       180
aagtagggtg agtcctcaaa atccgtatag ttggtgaagc cacagcactt gagccctttc
                                                                       240
atggtggtgt tecacaettg agtgaagtet teetgggaae cataatettt ettgatggea
                                                                       300
ggcactacca gcaacgtcag gaagtgctca gccattgtgg tgtacaccaa ggcgaccaca
                                                                       360
gcagctgcaa cctcagcaat gaagatgagg aggaggatga agaagaacgt cncgagggca
                                                                       420
cacttgctct ccgtcttagc accatagcag cccangaaac caagagcaaa gaccacaacg
                                                                       480
ccngctgcga atgaaagaaa ntacccacgt tgacaaactg catggccact ggacgacagt
                                                                       540
tggcccgaan atcttcagaa aagggatgcc ccatcgattg aacacccana tgcccactgc
                                                                       600
cnacaggget geneenenen gaaagaatga gecattgaag aaggatente ntggtettaa
                                                                       660
tgaactgaaa ccntgcatgg tggcccctgt tcagggctct tggcagtgaa ttctganaaa
                                                                       720
aaggaacngc ntnagccccc ccaaangana aaacaccccc gggtgttgcc ctgaattggc
                                                                       780
ggccaaggan ccctgccccn g
                                                                       801
      <210> 17
      <211> 740
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(740)
      <223> n = A,T,C or G
      <400> 17
gtgagagcca ggcgtccctc tgcctgccca ctcagtggca acacccggga gctgttttgt
                                                                        60
cctttgtgga gcctcagcag ttccctcttt cagaactcac tgccaagagc cctgaacagg
                                                                       120
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agccaccatg cagtgettea getteattaa gaccatgatg atcetettea atttgeteat

```
ctttctgtgt ggtgcagccc tgttggcagt gggcatctgg gtgtcaatcg atggggcatc
                                                                        240
etttetgaag atetteggge caetgtegte cagtgecatg cagtttgtea aegtgggeta
                                                                        300
cttectcatc gcagccggcg ttgtggtctt tgctcttggt ttcctgggct gctatggtgc
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taagacggag agcaagtgtg ccctcgtgac gttcttcttc atcctcctcc tcatcttcat
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tgctgaagtt gcagctgctg tggtcgcctt ggtgtacacc acaatggctg aaccattcct
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gacgttgctg gtantgcctg ccatcaanaa agattatggg ttcccaggaa aaattcactc
                                                                        540
aantntggaa caccnccatg aaaagggctc caatttctgn tggcttcccc aactataccg
                                                                        600
gaattttgaa aganteneec tactteeaaa aaaaaanant tgeetttnee eeenttetgt
                                                                        660
tgcaatgaaa acntcccaan acngccaatn aaaacctgcc cnnncaaaaa ggntcncaaa
                                                                        720
caaaaaant nnaagggttn
                                                                        740
      <210> 18
      <211> 802
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(802)
      <223> n = A, T, C \text{ or } G
      <400> 18
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                                                                        60
caaggtette cagetgeege acattaegea gggeaagage etecageaae actgeatatg
                                                                       120
ggatacactt tactttagca gccagggtga caactgagag gtgtcgaagc ttattcttct
                                                                       180
gagcctctgt tagtggagga agattccggg cttcagctaa gtagtcagcg tatgtcccat
                                                                       240
aagcaaacac tgtgagcagc cggaaggtag aggcaaagtc actctcagcc agctctctaa
                                                                       300
cattgggcat gtccagcagt tctccaaaca cgtagacacc agnggcctcc agcacctgat
                                                                       360
ggatgagtgt ggccagcgct gcccccttgg ccgacttggc taggagcaga aattgctcct
                                                                       420
ggttctgccc tgtcaccttc acttccgcac tcatcactgc actgagtgtg ggggacttgg
                                                                       480
geteaggatg tecagagaeg tggtteegee ceetenetta atgacacegn ceanneaace
                                                                       540
gteggetece geegantgng ttegtegtne etgggteagg gtetgetgge enetaettge
                                                                       600
aancttegte nggeeeatgg aatteaeene aceggaaetn gtangateea etnnttetat
                                                                       660
aaccggncgc caccgcnnnt ggaactccac tettnttncc tttacttgag ggttaaggtc
                                                                       720
accettnneg ttacettggt ccaaacentn centgtgteg anatngtnaa tenggneena
                                                                       780
tnccancene atangaagee ng
                                                                       802
      <210> 19
      <211> 731
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(731)
      <223> n = A, T, C or G
      <400> 19
cnaagettee aggtnaeggg eegenaance tgaceenagg tancanaang eagnengegg
                                                                        60
gagcccaccg tcacgnggng gngtctttat nggagggggc ggagccacat cnctggacnt
                                                                       120
```

entgacecca acteceence neneantgea gtgatgagtg cagaactgaa ggtnacgtgg

```
caggaaccaa gancaaanne tgeteennte caagteggen naqqqqqqqq qqetqqccae
                                                                       240
geneateent enagtgetgn aaageeeenn eetgtetaet tgtttggaga aengennnga
                                                                       300
catgcccagn gttanataac nggcngaqag tnantttqcc tctcccttcc qqctqcqcan
                                                                       360
cgngtntgct tagnggacat aacctgacta cttaactgaa cccnngaatc tnccncccct
                                                                       420
ccactaaget cagaacaaaa aacttegaca ccacteantt gteacetgne tgeteaagta
                                                                       480
aagtgtaccc catneccaat gtntgetnga ngetetgnee tgenttangt teggteetgg
                                                                       540
gaagacctat caattnaagc tatgtttctg actgcctctt gctccctgna acaancnacc
                                                                       600
cnncnntcca aggggggnc ggccccaat cccccaacc ntnaattnan tttanccccn
                                                                       660
ccccenggcc cggcctttta cnancntcnn nnacngggna aaaccnnngc tttncccaac
                                                                       720
nnaatccncc t
                                                                       731
      <210> 20
      <211> 754
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(754)
      \langle 223 \rangle n = A,T,C or G
      <400> 20
ttttttttt tttttttt taaaaacccc ctccattnaa tgnaaacttc cgaaattgtc
                                                                        60
caaccccctc ntccaaatnn ccntttccgg gngggggttc caaacccaan ttanntttgg
                                                                       120
annttaaatt aaatnttnnt tggnggnnna anccnaatgt nangaaagtt naacccanta
                                                                       180
tnancttnaa tncctggaaa ccngtngntt ccaaaaatnt ttaaccctta antccctccq
                                                                       240
aaatngttna nggaaaaccc aanttctcnt aaggttgttt gaaggntnaa tnaaaanccc
                                                                       300
nnccaattgt ttttnqccac qcctqaatta attqqnttcc qntqttttcc nttaaaanaa
                                                                       360
ggnnancece ggttantnaa teececenne eecaattata eeganttttt ttngaattgg
                                                                       420
ganecenegg gaattaaegg ggnnnnteee tnttgggggg enggnneeee eecenteggg
                                                                       480
ggttngggnc aggncnnaat tgtttaaggg tccgaaaaat ccctccnaga aaaaaanctc
                                                                       540
ccaggntgag nntngggttt ncccccccc canggcccct ctcgnanagt tggggtttgg
                                                                       600
ggggcctggg attttntttc ccctnttncc tcccccccc ccnggganag aggttngngt
                                                                       660
tttgntcnnc ggccccnccn aaganctttn ccganttnan ttaaatccnt qcctnqqcqa
                                                                       720
agtcenttgn agggntaaan qqccccctnn cqqq
                                                                       754
      <210> 21
      <211> 755
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(755)
      <223> n = A, T, C or G
      <400> 21
atcancccat gaccccnaac nngggaccnc tcanccggnc nnncnaccnc cggccnatca
                                                                        60
nngtnagnnc actnonnttn natcacnece encenactae gecenenane enaegeneta
                                                                       120
nncanatnce actganngcg cgangtngan ngagaaanct nataccanag ncaccanacn
                                                                       180
```

ccagctgtcc nanaangcct nnnatacngg nnnatccaat ntqnancctc cnaagtattn

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nncnncanat gattttcctn anccqattac contneccec tanccectcc cecccaacna
                                                                        300
cgaaggenet ggneenaagg nngegnenee eegetagnte eeenneaagt eneneneeta
                                                                        360
aactcanccn nattacnege ttentgagta teactceecg aateteacce tactcaacte
                                                                        420
aaaaanatcn gatacaaaat aatncaagcc tgnttatnac actntgactg ggtctctatt
                                                                        480
ttagnggtcc ntnaancntc ctaatacttc cagtetnect tenecaattt cenaangget
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ctttcngaca gcatnttttg gttcccnntt gggttcttan ngaattgccc ttcntngaac
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gggetentet tttccttcgq ttancctqqn ttennccqqc caqttattat ttcccntttt
                                                                        660
aaattentne entttanttt tggenttena aaceeeegge ettgaaaaeg geeeeetggt
                                                                        720
aaaaggttgt tttganaaaa tttttgtttt gttcc
                                                                        755
      <210> 22
      <211> 849
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(849)
      <223> n = A, T, C \text{ or } G
      <400> 22
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                                                                         60
acgctnggan taangcgacc cganttctag gannencect aaaatcanac tgtgaagatn
                                                                        120
atectgnnna eggaanggte aceggnngat nntqetaggg tgncenetee cannnenttn
                                                                        180
cataacteng nggccctgcc caccaccttc ggcggcccng ngnccgggcc cgggtcattn
                                                                        240
gnnttaaccn cactnigena neggttteen neecenneng accenqueqa teeqqqqtne
                                                                        300
tetgtettee cetgnagnen anaaantggg ceneggneee etttaceeet nnacaageea
                                                                        360
engeenteta neenengeee eeeeteeant nngggggaet geenannget eegttnetng
                                                                        420
nnacccennn gggtncctcg gttgtcgant cnaccgnang ccanggattc cnaaggaagg
                                                                        480
tgcgttnttg gcccctaccc ttcqctncqq nncacccttc ccqacnanqa nccqctcccq
                                                                        540
channeging detended caacacege netentengt negginned deceacege
                                                                        600
necetenene ngnegnanen eteeneenee gteteannea eeaceeegee eegeeaggee
                                                                        660
ntcanccacn ggnngacnng nagcnennte geneegegen gegneneeet egeenengaa
                                                                        720
ctncntcngg ccantnncgc tcaanccnna cnaaacgccg ctgcgcggcc cgnaqcqncc
                                                                        780
necteenega gteeteeegn etteenacee angnntteen egaggaeaen nnaceeegee
                                                                        840
nncangcgg
                                                                        849
      <210> 23
      <211> 872
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(872)
      <223> n = A, T, C \text{ or } G
      <400> 23
gegeaaacta tacttegete gnactegtge geetegetne tetttteete egeaaceatg
                                                                         60
tctgacnanc ccgattnggc ngatatcnan aagntcganc agtccaaact gantaacaca
                                                                        120
```

cacacnenan aganaaatee netgeettee anagtanaen attgaaenng agaaeeange

```
nggcgaatcg taatnaggcg tgcgccgcca atntgtcncc gtttattntn ccaqcntcnc
                                                                       240
ctnccnaccc tacntcttcn nagctgtcnn acccctngtn cgnaccccc naggtcqqqa
                                                                       300
tegggtttnn nntgacegng enneceetee eccenteeat nacganeene eegeaceaee
                                                                       360
nanngenege neceegnnet ettegeenee etgteetntn eeeetgtnge etggenengn
                                                                       420
accgcattga ccctcgccnn ctncnngaaa ncgnanacgt ccgggttgnn annancgctg
                                                                       480
tgggnnngcg tctgcnccgc gttccttccn ncnncttcca ccatcttcnt tacnqqqtct
                                                                       540
conegeente tennneaene cetgggaege thteethtge ceceetthae teceeceett
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cgncgtgncc cgnccccacc ntcatttnca nacgntcttc acaannncct ggntnnctcc
                                                                       660
cnancngncn gtcanccnag ggaagggngg ggnnccnntg nttgacgttg nggngangtc
                                                                       720
cgaanantcc tcnccntcan cnctacccct cgggcgnnct ctcngttncc aacttancaa
                                                                       780
nteteccecy ngngenente teageetene ceneceenet etetgeanty tnetetgete
                                                                       840
tnaccnntac gantnttcgn cnccctcttt cc
                                                                       872
      <210> 24
      <211> 815
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(815)
      <223> n = A,T,C or G
      <400> 24
gcatgcaagc ttgagtattc tatagngtca cctaaatanc ttggcntaat catggtcnta
                                                                        60
nctgncttcc tgtgtcaaat gtatacnaan tanatatgaa tctnatntga caaganngta
                                                                       120
tentneatta gtaacaantg tnntgteeat cetgtengan canatteeca tnnattnegn
                                                                       180
cgcattcncn gcncantatn taatngggaa ntcnnntnnn ncaccnncat ctatcntncc
                                                                       240
genecetgae tggnagagat ggatnantte tnntntgaee nacatgttea tettggattn
                                                                       300
aanancecce egengneeae eggttngnng enageennte ecaagacete etgtqqaqqt
                                                                       360
aacctgcgtc aganncatca aacntgggaa acccgcnncc angtnnaagt ngnnncanan
                                                                       420
gatecegtee aggnttnace atceettene agegeeecet ttngtgeett anagngnage
                                                                       480
gtgtccnanc cnctcaacat ganacgcgcc agnccanccg caattnggca caatgtcgnc
                                                                       540
gaacccccta gggggantna tncaaanccc caggattgtc cncncangaa atcccncanc
                                                                       600
cccnccctac ccnnctttgg gacngtgacc aantcccgga gtnccaqtcc ggccnqnctc
                                                                       660
ccccaccggt nnccntgggg gggtgaanet cngnntcanc cngncgaggn ntcgnaagga
                                                                       720
accggneetn ggnegaanng anenntenga agngeenent eqtataacce ecceteneca
                                                                       780
nccnacngnt agntcccccc engggtnegg aangg
                                                                       815
      <210> 25
      <211> 775
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(775)
      <223> n = A, T, C \text{ or } G
      <400> 25
cegagatgte tegeteegtg geettagetg tgetegeget actetetett tetggeetqq
```

```
aggetateca gegtaeteca aagatteagg tttaeteaeg teatecagea gagaatggaa
                                                                        120
 agtcaaattt cctgaattgc tatqtqtctq qqtttcatcc atccqacatt qaanttqact
                                                                        180
 tactgaagaa tgganagaga attgaaaaag tggagcattc agacttgtct ttcagcaagg
                                                                        240
 actggtettt etatetentg tactacaetg aatteaceee caetgaaaaa gatgagtatg
                                                                        300
 cctgccgtgt gaaccatgtg actttgtcac agcccaagat agttaagtgg gatcgagaca
                                                                        360
 tgtaagcagn cnncatggaa gtttgaagat gccgcatttg gattggatga attccaaatt
                                                                        420
 ctgcttgctt gcnttttaat antgatatgc ntatacaccc taccctttat qnccccaaat
                                                                        480
 tgtaggggtt acatnantgt tenentngga catgatette etttataant eeneentteg
                                                                        540
 aattgcccgt cncccngttn ngaatgtttc cnnaaccacg gttgqctccc ccaggtcncc
                                                                        600
 tettaeggaa gggeetggge enetttneaa ggttggggga acenaaaatt tenettntge
                                                                        660
 conceencea ennicitigng increantit ggaaccette enatteeect tggeetenna
                                                                        720
nccttnncta anaaaacttn aaancgtngc naaanntttn acttcccccc ttacc
                                                                        775
       <210> 26
       <211> 820
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(820)
       <223> n = A, T, C \text{ or } G
       <400> 26
 anattantac agtgtaatct tttcccagag gtgtgtanag ggaacggggc ctagaggcat
                                                                         60
 cccanagata nettatanca acagtgettt gaccaagage tgetgggeae attteetgea
                                                                        120
gaaaaggtgg cggtccccat cactcctcct ctcccatagc catcccagag gggtgagtag
                                                                        180
 ccatcangcc ttcggtggga gggagtcang gaaacaacan accacagagc anacagacca
                                                                        240
ntgatgacca tgggcgggag cgagcctctt ccctgnaccg gggtggcana nganagccta
                                                                        300
nctgaggggt cacactataa acgttaacga ccnagatnan cacctgcttc aagtgcaccc
                                                                        360
 ttcctacctg acnaccagng accnnnaact gengeetggg gacagenetg ggancageta
                                                                        420
 acnnageact cacetgeece eccatggeeg thegenteec tggteetgne aagggaaget
                                                                        480
 ccctgttgga attncgggga naccaaggga nccccctcct ccanctgtga aggaaaaann
                                                                        540
 gatggaattt tnecetteeg geennteece tetteettta eaegeeeet nntactente
                                                                        600
 tecetetntt nteetgnene aettttnace cennnattte eettnattga teggannetn
                                                                        660
ganattecae tnnegeetne entenateng naanaenaaa naetntetna eeenqqqqat
                                                                        720
gggnnceteg nteatectet etttttenet aceneenntt etttgeetet eettngatea
780tccaaccntc gntggccntn cccccccnnn tcctttnccc
                                                                          820
       <210> 27
       <211> 818
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(818)
       <223> n = A, T, C or G
       <400> 27
tetgggtgat ggeetettee teeteaggga eetetgaetg etetgggeea aagaatetet
                                                                         60
```

```
tgtttettet cegageeeca ggeageggtg atteageeet geecaacetg attetgatga
                                                                       120
ctgcggatgc tgtgacggac ccaaggggca aatagggtcc cagggtccag ggaggggcgc
                                                                       180
etgetgagea etteegeece teaccetgee cageceetge catgagetet gggetgggte
                                                                       240
teegeeteea gggttetget etteeangea ngeeancaag tggegetggg eeacaetgge
                                                                       300
ttcttcctgc cccntccctg gctctgantc tctgtcttcc tgtcctgtgc angcnccttg
                                                                       360
gatctcagtt tccctcnctc anngaactct gtttctgann tcttcantta actntgantt
                                                                       420
tatnaccnan tggnctgtnc tgtcnnactt taatgggccn gaccggctaa tccctccctc
                                                                       480
nctcccttcc anttennnna accngettne ententetee centaneeeq cengggaane
                                                                       540
ctcctttgcc ctnaccangg gccnnnaccg cccntnnctn ggggggcnng gtnnctncnc
                                                                       600
etgntnnece enetenennt theetegtee ennennegen nngeanntte nengteeenn
                                                                       660
tnnctcttcn ngtntcgnaa ngntcncntn tnnnnngncn ngntnntncn tccctctcnc
                                                                       720
cnnntgnang tnnttnnnnc nengnneece nnnnennnnn nggnnntnnn tetnenenge
                                                                       780
cccnnccccc ngnattaagg cctccnntct ccgqccnc
                                                                       818
      <210> 28
      <211> 731
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(731)
      <223> n = A,T,C or G
      <400> 28
aggaagggcg gagggatatt gtangggatt gagggatagg agnataangg gggaggtgtg
                                                                        60
teceaacatg anggtgnngt tetettttga angagggttg ngtttttann eenggtgggt
                                                                       120
gattnaaccc cattgtatgg agnnaaaggn tttnagggat ttttcggctc ttatcagtat
                                                                       180
ntanattcct gtnaatcgga aaatnatntt tcnncnggaa aatnttgctc ccatccgnaa
                                                                       240
attneteceg ggtagtgeat nttngggggn engecangtt teccaggetg etanaategt
                                                                       300
actaaagntt naagtgggan tncaaatgaa aacctnncac agagnatccn tacccgactg
                                                                       360
tnnnttncct tegecetntg actetgenng ageccaatac cenngngnat gtenecengn
                                                                       420
nnngcgncnc tgaaannnnc tcgnggctnn gancatcang gggtttcgca tcaaaagcnn
                                                                       480
egttteneat naaggeactt tngceteate caacenetng eeetenneea tttngeegte
                                                                       540
nggttenect aegetnntng encetnnntn ganattttne eegeetnggg naanceteet
                                                                       600
gnaatgggta gggnettnte ttttnacenn qnqqtntact aatennetne acqentnett
                                                                       660
tetenacece ceceetttt caateecane ggenaatggg gteteecenn eganggggg
                                                                       720
nnncccannc c
                                                                       731
      <210> 29
      <211> 822
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(822)
      <223> n = A,T,C or G
      <400> 29
actagtccag tgtggtggaa ttccattgtg ttggggncnc ttctatgant antnttagat
                                                                        60
```

```
cgctcanacc tcacancctc ccnacnangc ctataangaa nannaataga nctgtncnnt
                                                                       120
atntntacnc teatannect ennnaceeae teeetettaa eeentactgt geetatngen
                                                                       180
tnnctantct ntgccgcctn cnanccaccn gtgggccnac cncnngnatt ctcnatctcc
                                                                       240
tenecatntn geetananta ngtneatace etatacetae necaatgeta nnnetaanen
                                                                       300
tccatnantt annntaacta ccactgacnt ngactttcnc atnanctcct aatttgaatc
                                                                       360
tactctgact cccacngcct annnattagc ancntccccc nacnatntct caaccaaatc
                                                                       420
ntcaacaacc tatctanctq ttcnccaacc nttncctccq atccccnnac aacccccctc
                                                                       480
ccaaataccc nccacctqac ncctaacccn caccatcccq gcaagccnan ggncatttan
                                                                       540
ccactggaat cacnatngga naaaaaaaac ccnaactctc tancncnnat ctccctaana
                                                                       600
aatneteetn naatttaetn neantneeat caaneecaen tgaaaennaa eecetgtttt
                                                                       660
tanatecett etttegaaaa eenaeeettt annneeeaae etttngggee eeeeenetne
                                                                       720
ccnaatgaag gncncccaat cnangaaacg nccntgaaaa ancnaggcna anannntccg
                                                                       780
canatectat ceettanttn ggggneeett neeengggee ee
                                                                       822
      <210> 30
      <211> 787
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(787)
      <223> n = A, T, C or G
      <400> 30
eggeegeetg etetggeaca tgeeteetga atggeateaa aagtgatgga etgeecattg
                                                                        60
ctagagaaga cettetetee taetgteatt atggageeet geagaetgag ggeteeeett
                                                                       120
qtctqcaqqa tttqatqtct qaaqtcqtqq aqtqtqqctt ggaqctcctc atctacatna
                                                                       180
qctqqaaqcc ctqqaqqqcc tctctcqcca qcctcccct tctctccacq ctctccangq
                                                                       240
acaccagggg ctccaggcag cccattattc ccagnangac atggtgtttc tccacgcgga
                                                                       300
cccatggggc ctgnaaggcc agggtctcct ttgacaccat ctctcccgtc ctgcctggca
                                                                       360
ggccgtggga tccactantt ctanaacggn cgccaccncg gtgggagctc cagcttttgt
                                                                       420
tecenttaat gaaggttaat tgenegettg gegtaateat nggteanaae tnttteetgt
                                                                       480
gtgaaattgt ttntcccctc ncnattccnc ncnacatacn aacccggaan cataaagtgt
                                                                       540
                                                                       600
taaaqcctqq qqqtnqcctn nnqaatnaac tnaactcaat taattgcgtt ggctcatggc
ccqctttccn ttcnqqaaaa ctqtcntccc ctqcnttnnt gaatcgqcca cccccnggg
                                                                       660
aaaageggtt tgenttttng ggggnteett cenetteece eetenetaan eeetnegeet
                                                                       720
cggtcgttnc nggtngcggg gaangggnat nnnctcccnc naagggggng agnnngntat
                                                                       780
                                                                       787
ccccaaa
      <210> 31
      <211> 799
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(799)
      <223> n = A, T, C \text{ or } G
      <400> 31
```

```
ttttttttt ttttttggc gatgctactg tttaattgca ggaggtgggg gtgtgtgtac
                                                                      60
catgtaccag ggctattaga agcaagaagg aaggagggag ggcagagcgc cctgctgagc
                                                                     120
aacaaaggac teetgeagee ttetetgtet gtetettgge geaggeacat ggggaggeet
                                                                     180
cccgcagggt gggggccacc agtccagggg tgggagcact acanggggtg ggagtgggtg
                                                                     240
gtggctggtn cnaatggcct gncacanatc cctacgattc ttgacacctg gatttcacca
                                                                     300
ggggaccttc tgttctccca nggnaacttc ntnnatctcn aaagaacaca actgtttctt
                                                                     360
engeanttet ggetgtteat ggaaageaca ggtgteenat ttnggetggg acttggtaca
                                                                     420
tatggttccg gcccacctct cccntcnaan aagtaattca ccccccccn ccntctnttq
                                                                     480
cctgggccct taantaccca caccggaact canttantta ttcatcttng gntgggcttg
                                                                     540
ntnatencen cetgaangeg ceaagttgaa aggeeaegee gtneeenete eecataqnan
                                                                     600
nttttnncnt canctaatgc ccccccnggc aacnatccaa tcccccccn tgggggccc
                                                                     660
ageceangge eccegneteg ggnnneengn enegnantee ecaggntete ceantengne
                                                                     720
connigence ecegeacyca gaacanaagg ntngageene egeanninnin ngqtnicnae
                                                                     780
ctcgccccc ccnncgnng
                                                                     799
      <210> 32
      <211> 789
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
     <222> (1)...(789)
      <223> n = A,T,C or G
      <400> 32
60
ttttnccnag ggcaggttta ttgacaacct cncgggacac aancaggctg gggacaggac
                                                                     120
ggcaacaggc teeggeggeg geggeggegg cectacetge ggtaccaaat ntqcaqeete
                                                                     180
egeteeeget tgatntteet etgeagetge aggatgeent aaaacaggge eteggeentn
                                                                     240
ggtgggcacc ctgggatttn aatttccacg ggcacaatgc ggtcgcancc cctcaccacc
                                                                     300
nattaggaat agtggtntta cccnccnccg ttggcncact ccccntggaa accacttntc
                                                                     360
geggeteegg catetggtet taaacettge aaacnetggg geeetetttt tggttantnt
                                                                     420
ncengecaca atcatnacte agactggene gggetggece caaaaaanen eeccaaaace
                                                                     480
ggnccatgtc ttnncggggt tgctgcnatn tncatcacct cccqqqcnca ncaqqncaac
                                                                     540
ccaaaagttc ttgnggcccn caaaaaanct ccggggggnc ccagtttcaa caaagtcatc
                                                                     600
ccccttggcc cccaaatcct cccccgntt nctgggtttg ggaacccacg cctctnnctt
                                                                     660
tggnnggcaa gntggntccc ccttcgggcc cccggtgggc ccnnctctaa ngaaaacncc
                                                                     720
ntcctnnnca ccatccccc nngnnacgnc tancaangna tccctttttt tanaaacggg
                                                                     780
cccccncg
                                                                     789
      <210> 33
      <211> 793
      <212> DNA
      <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(793)
     \langle 223 \rangle n = A,T,C or G
```

```
<400> 33
                                                                         60
gacagaacat gttggatggt ggagcacctt tctatacgac ttacaggaca gcagatgggg
                                                                        120
aattcatggc tgttggagca atanaacccc agttctacga gctgctgatc aaaggacttg
gactaaagtc tgatgaactt cccaatcaga tgagcatgga tgattggcca gaaatgaana
                                                                        180
agaagtttgc agatgtattt gcaaagaaga cgaaggcaga gtggtgtcaa atctttgacg
                                                                        240
gcacagatgc ctgtgtgact ccggttctga cttttgagga ggttgttcat catgatcaca
                                                                        300
                                                                        360
acaangaacg gggctcgttt atcaccantg aggagcagga cgtgagcccc cgccctgcac
                                                                        420
ctctgctgtt aaacacccca gccatccctt ctttcaaaag ggatccacta cttctagagc
                                                                        480
ggncgccacc gcggtggagc tccagctttt gttcccttta gtgagggtta attgcgcgct
tggcgtaatc atggtcatan ctgtttcctg tgtgaaattg ttatccgctc acaattccac
                                                                        540
acaacatacg anccggaagc atnaaatttt aaagcctggn ggtngcctaa tgantgaact
                                                                        600
nactcacatt aattggettt gegeteactg eeegetttee agteeggaaa acetgteett
                                                                        660
gccagctgcc nttaatgaat cnggccaccc cccggggaaa aggcngtttg cttnttgggg
                                                                        720
                                                                        780
egenettece getttetege tteetgaant eetteeece ggtetttegg ettgeggena
                                                                        793
acggtatcna cct
      <210> 34
      <211> 756
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(756)
      \langle 223 \rangle n = A,T,C or G
      <400> 34
                                                                         60
gccgcgaccg gcatgtacga gcaactcaag ggcgagtgga accgtaaaag ccccaatctt
ancaagtgcg gggaanagct gggtcgactc aagctagttc ttctggagct caacttcttg
                                                                        120
                                                                        180
ccaaccacag ggaccaagct gaccaaacag cagctaattc tggcccgtga catactggag
ateggggeee aatggageat cetaegeaan gacateeeet eettegageg etaeatggee
                                                                        240
caqctcaaat qctactactt tgattacaan gagcagctcc ccgagtcagc ctatatgcac
                                                                        300
cagetettgg geeteaacet eetetteetg etgteecaga acegggtgge tgantnecae
                                                                        360
                                                                        420
acgganttgg ancggctgcc tgcccaanga catacanacc aatgtctaca tcnaccacca
                                                                        480
gtgtcctgga gcaatactga tgganggcag ctaccncaaa gtnttcctgg ccnagggtaa
catececege egaqagetae acettettea ttgacateet getegacaet ateagggatg
                                                                        540
aaaatcgcng ggttgctcca gaaaggctnc aanaanatcc ttttcnctga aggcccccgg
                                                                        600
atnonotagt notagaatog geoegecate geggtggane etceaacett tegttneeet
                                                                        660
ttactgaggg ttnattgccg cccttggcgt tatcatggtc acnccngttn cctgtgttga
                                                                        720
aattnttaac ccccacaat tccacgccna cattng
                                                                        756
      <210> 35
      <211> 834
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(834)
      \langle 223 \rangle n = A,T,C or G
```

```
<400> 35
ggggatctct anatchacct gnatgcatgg ttgtcggtgt ggtcgctgtc gatgaanatg
                                                                         60
aacaggatet tgeeettgaa getetegget getgtnttta agttgeteag tetgeegtea
                                                                        120
tagtcagaca cnctcttggg caaaaaacan caggatntga gtcttgattt cacctccaat
                                                                        180
aatettengg getgtetget eggtgaaete gatgaenang ggeagetggt tgtgtntgat
                                                                        240
aaantccanc angtteteet tggtgacete ceetteaaag ttgtteegge etteateaaa
                                                                        300
cttctnnaan angannance canctttgtc gagctggnat ttgqanaaca cqtcactqtt
                                                                        360
ggaaactgat cccaaatggt atgtcatcca tegectetge tgcctgcaaa aaacttgett
                                                                        420
ggeneaaate egacteeeen teettgaaag aageenatea eacceeete eetqqaetee
                                                                        480
nncaangact ctnccgctnc cccntccnng cagggttggt ggcannccgg gcccntgcgc
                                                                        540
ttottcagcc agttcacnat nttcatcagc ccctctgcca gctqttntat tccttqqqqq
                                                                        600
ggaancegte tetecettee tgaannaact ttgacegtng gaatageege gentencent
                                                                        660
acnincitggg cegggticaa anteceteen tignennien eetegggeea tietggatti
                                                                        720
ncenaacttt ttccttcccc cncccencgg ngtttggntt tttcatnggg ccccaactct
                                                                        780
getnttggee anteceetgg gggentntan enceeeetnt ggteeentng ggee
                                                                        834
      <210> 36
      <211> 814
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(814)
      <223> n = A, T, C \text{ or } G
      <400> 36
eggnegettt cengeegege eeegttteea tgacnaagge teeetteang ttaaataenn
                                                                         60
cctagnaaac attaatgggt tgctctacta atacatcata cnaaccagta agcctgccca
                                                                        120
naacgccaac tcaggccatt cctaccaaag gaagaaaggc tggtctctcc acccctgta
                                                                        180
ggaaaggcct gccttgtaag acaccacaat ncggctgaat ctnaagtctt gtgttttact
                                                                        240
aatggaaaaa aaaaataaac aanaggtttt gttctcatgg ctgcccaccg cagcctggca
                                                                        300
ctaaaacanc ccagcgctca cttctgcttg ganaaatatt ctttgctctt ttggacatca
                                                                        360
ggettgatgg tateactgee aenttteeae eeagetggge neeetteeee catntttgte
                                                                        420
antganctgg aaggeetgaa nettagtete caaaagtete ngeecacaag accqqccace
                                                                        480
aggggangtc ntttncagtg gatctgccaa anantacccn tatcatcnnt qaataaaaaq
                                                                        540
gcccctgaac ganatgcttc cancancett taagacccat aatcetngaa ccatggtgcc
                                                                        600
etteeggtet gateenaaag gaatgtteet gggteeeant eesteettig tinettaegt
                                                                        660
tgtnttggac centgetngn atnacecaan tganatecee ngaageacee tneeeetgge
                                                                       720
atttganttt entaaattet etgeeetaen netgaaagea enatteeetn ggeneenaan
                                                                        780
ggngaactca agaaggtctn ngaaaaacca cncn
                                                                        814
      <210> 37
      <211> 760
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(760)
      <223> n = A, T, C \text{ or } G
```

```
<400> 37
                                                                        60
gcatgctgct cttcctcaaa gttgttcttg ttgccataac aaccaccata ggtaaagcgg
gcgcagtgtt cgctgaaggg gttgtagtac cagcgcggga tgctctcctt gcagagtcct
                                                                       120
                                                                       180
gtgtctggca ggtccacgca atgccctttg tcactgggga aatggatgcg ctggagctcg
tenaaneeae tegtqtattt tteaeangea geeteeteeg aagenteegg geagttgggg
                                                                       240
                                                                       300
qtqtcqtcac actccactaa actqtcqatn cancagecca ttgctgcage ggaactgggt
gggctgacag gtgccagaac acactggatn ggcctttcca tggaagggcc tgggggaaat
                                                                       360
                                                                       420
cncctnance caaactgeet etcaaaggee acettgeaca eccegacagg etagaaatge
                                                                       480
actettette ecaaaggtag ttgttettgt tgeecaagea neeteeanea aaceaaaane
ttgcaaaatc tgctccgtgg gggtcatnnn taccanggtt ggggaaanaa acccggcngn
                                                                       540
ganccncctt gtttgaatgc naaggnaata atcctcctgt cttgcttggg tggaanagca
                                                                       600
caattgaact gttaacnttg ggccgngttc cnctngggtg gtctgaaact aatcaccgtc
                                                                       660
actggaaaaa ggtangtgcc ttccttgaat tcccaaantt cccctngntt tgggtnnttt
                                                                       720
                                                                       760
ctcctctncc ctaaaaatcg tnttcccccc ccntanggcg
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      <211> 724
      <212> DNA
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      <220>
      <221> misc feature
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      <223> n = A,T,C or G
      <400> 38
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cttccnaaat tgtccaaccc cctcnnccaa atnnccattt ccgggggggg gttccaaacc
                                                                       120
caaattaatt ttqqanttta aattaaatnt tnattnqqqq aanaanccaa atgtnaagaa
                                                                       180
aatttaaccc attatnaact taaatncctn gaaacccntg gnttccaaaa atttttaacc
                                                                       240
cttaaatccc tccgaaattg ntaanggaaa accaaattcn cctaaggctn tttgaaggtt
                                                                       300
ngatttaaac ccccttnant tnttttnacc cnngnctnaa ntatttngnt tccggtgttt
                                                                       360
                                                                       420
tcctnttaan cntnggtaac tcccgntaat gaannnccct aanccaatta aaccgaattt
tttttgaatt ggaaattccn ngggaattna ccggggtttt tcccntttgg gggccatncc
                                                                       480
                                                                       540
cccnctttcq qqqtttqqqn ntaqqttqaa tttttnnang ncccaaaaaa ncccccaana
aaaaaactcc caagnnttaa ttngaatntc ccccttccca ggccttttgg gaaaggnggg
                                                                       600
tttntggggg cengggantt entteeceen ttneeneece eeeecenggt aaanggttat
                                                                       660
ngnntttggt ttttgggccc cttnanggac cttccggatn gaaattaaat ccccgggncg
                                                                       720
                                                                       724
gccg
      <210> 39
      <211> 751
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(751)
      <223> n = A,T,C or G
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<400> 39
ttttttttt tttttctttg ctcacattta atttttattt tgatttttt taatgctgca
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caacacaata tttatttcat ttgtttcttt tatttcattt tatttgtttg ctgctgctgt
                                                                       120
tttatttatt tttactgaaa gtgagaggga acttttgtgg ccttttttcc tttttctgta
                                                                       180
ggccgcctta agctttctaa atttggaaca tctaagcaag ctgaanggaa aagggggttt
                                                                       240
cgcaaaatca ctcgggggaa nggaaaggtt gctttgttaa tcatgcccta tggtgggtga
                                                                       300
ttaactgctt gtacaattac ntttcacttt taattaattg tgctnaangc tttaattana
                                                                       360
cttgggggtt ccctccccan accaaccccn ctgacaaaaa gtgccngccc tcaaatnatg
                                                                       420
teceggennt enttgaaaca caengengaa ngtteteatt nteecenene eaggtnaaaa
                                                                       480
tqaaqqqtta ccatntttaa cnccacctcc acntqqcnnn qcctqaatcc tcnaaaancn
                                                                       540
ccctcaanen aattnetnng ccccggtene gentnngtee eneceggget eegggaantn
                                                                       600
cacccccnga annountnuc naacnaaatt ccgaaaatat tcccnntcnc tcaattcccc
                                                                       660
cnnagaetht cetennenan encaatttte ttttnnteae gaaenegnne ennaaaatgn
                                                                       720
nnnncncctc cnctngtccn naatcnccan c
                                                                       751
      <210> 40
      <211> 753
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      <213> Homo sapien
      <220>
      <221> misc feature
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      <223> n = A,T,C or G
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agatgaaaac ccccccgaga cagcagcact gcaactgcca agcagccggg gtaggagggg
                                                                       120
cgccctatgc acagctgggc ccttgagaca gcagggcttc gatgtcaggc tcgatgtcaa
                                                                       180
tggtctggaa gcggcggctg tacctgcgta ggggcacacc gtcagggccc accaggaact
                                                                       240
teteaaagtt eeaggeaaen tegttgegae acaeeggaga eeaggtgatn agettggggt
                                                                       300
cggtcataan cgcggtggcg tcgtcgctgg gagctggcag ggcctcccgc aggaaggcna
                                                                       360
ataaaaggtg cgccccgca ccgttcanct cgcacttctc naanaccatg angttgggct
                                                                       420
cnaacccacc accanneegg actteettga nggaatteec aaatetette gntettggge
                                                                       480
ttctnctgat gccctanctg gttqcccngn atgccaanca nccccaance ccggggtcct
                                                                       540
aaancacccn cctcctcntt tcatctgggt tnttntcccc ggaccntggt tcctctcaag
                                                                       600
gganeceata tetenacean tacteacent necececent gnnacecane ettetanngn
                                                                       660
ttcccncccg ncctctggcc cntcaaanan gcttncacna cctgggtctg ccttccccc
                                                                       720
tnecetatet gnacecenen tttgtetean tnt
                                                                       753
      <210> 41
      <211> 341
      <212> DNA
      <213> Homo sapien
      <400> 41
actatatcca tcacaacaga catgettcat cecatagaet tettgacata gettcaaatg
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agtgaaccca tccttgattt atatacatat atgttctcag tattttggga gcctttccac
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ttctttaaac cttgttcatt atgaacactg aaaataggaa tttgtgaaga gttaaaaagt
                                                                       180
tatagcttgt ttacgtagta agtttttgaa gtctacattc aatccagaca cttagttgag
                                                                       240
tgttaaactg tgatttttaa aaaatatcat ttgagaatat tctttcagag gtattttcat
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341
ttttactttt tgattaattg tgttttatat attagggtag t
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      <211> 101
      <212> DNA
      <213> Homo sapien
      <400> 42
acttactqaa tttaqttctg tgctcttcct tatttagtgt tgtatcataa atactttgat
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                                                                       101
gtttcaaaca ttctaaataa ataattttca gtggcttcat a
      <210> 43
      <211> 305
      <212> DNA
      <213> Homo sapien
      <400> 43
                                                                        60
acatetttgt tacagtetaa gatgtgttet taaateacea tteetteetg gteeteacee
                                                                       120
tccagggtgg tctcacactg taattagagc tattgaggag tctttacagc aaattaagat
tcagatgect tgetaagtet agagttetag agttatgttt cagaaaagtet aagaaaceca
                                                                       180
cctcttgaga ggtcagtaaa gaggacttaa tatttcatat ctacaaaatg accacaggat
                                                                       240
tggatacaga acgagagtta tcctggataa ctcagagctg agtacctgcc cgggggccgc
                                                                       300
                                                                       305
tcgaa
      <210> 44
      <211> 852
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(852)
      <223> n = A, T, C or G
      <400> 44
                                                                        60
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gattatttgg tgtgtgtttt ggtttgtgtc caaagtattg gcagcttcag ttttcatttt
                                                                       120
ctctccatcc tcgggcattc ttcccaaatt tatataccag tcttcgtcca tccacacgct
                                                                       180
ccaqaatttc tcttttgtag taatatctca tagctcggct gagcttttca taggtcatgc
                                                                        240
tgctgttgtt cttcttttta ccccataget gagccactgc ctctgatttc aagaacctga
                                                                        300
agacgccctc agatcggtct tcccatttta ttaatcctgg gttcttgtct gggttcaaga
                                                                        360
ggatgtegeg gatgaattee cataagtgag teeetetegg gttgtgettt ttggtgtgge
                                                                        420
acttggcagg ggggtcttgc tcctttttca tatcaggtga ctctgcaaca ggaaggtgac
                                                                        480
tggtggttgt catggagatc tgagcccggc agaaagtttt gctgtccaac aaatctactg
                                                                        540
                                                                        600
tgctaccata gttggtgtca tataaatagt tctngtcttt ccaggtgttc atgatggaag
                                                                        660
gctcagtttg ttcagtcttg acaatgacat tgtgtgtgga ctggaacagg tcactactgc
                                                                        720
actggccgtt ccacttcaga tgctgcaagt tgctgtagag gagntgcccc gccgtccctg
ccqcccqqqt qaactcctgc aaactcatgc tgcaaaggtg ctcgccgttg atgtcgaact
                                                                        780
cntggaaagg gatacaattg gcatccagct ggttggtgtc caggaggtga tggagccact
                                                                        840
                                                                        852
cccacacctg gt
```

```
<210> 45
       <211> 234
       <212> DNA
       <213> Homo sapien
       <400> 45
 acaacagacc cttgctcgct aacgacctca tgctcatcaa gttggacgaa tccgtgtccg
                                                                          60
 agtctgacac catccggagc atcagcattg cttcgcagtg ccctaccgcg gggaactctt
                                                                         120
 gcctcgtttc tggctggggt ctgctggcga acggcagaat gcctaccgtg ctgcagtgcg
                                                                         180
 tgaacgtgtc ggtggtgtct gaggaggtct gcagtaagct ctatgacccg ctgt
                                                                         234
       <210> 46
       <211> 590
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(590)
       <223> n = A, T, C \text{ or } G
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                                                                         60
atttgatagc aatattttgg agattacaga gttttagtaa ttaccaatta cacagttaaa
                                                                         120
aagaagataa tatatteeaa geanataeaa aatatetaat gaaagateaa ggeaggaaaa
                                                                        180
tgantataac taattgacaa tggaaaatca attttaatgt gaattgcaca ttatccttta
                                                                        240
aaagctttca aaanaaanaa ttattgcagt ctanttaatt caaacagtgt taaatggtat
                                                                        300
caggataaan aactgaaggg canaaagaat taattttcac ttcatgtaac ncacccanat
                                                                        360
ttacaatggc ttaaatgcan ggaaaaagca gtggaagtag ggaagtantc aaggtctttc
                                                                        420
tggtctctaa tctgccttac tctttgggtg tggctttgat cctctggaga cagctgccag
                                                                        480
ggctcctgtt atatccacaa tcccagcagc aagatgaagg gatgaaaaag gacacatgct
                                                                        540
geetteettt gaggagaett eateteaetg geeaacaete agteacatgt
                                                                        590
      <210> 47
      <211> 774
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(774)
      <223> n = A,T,C \text{ or } G
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tgaacagaat tttcctgnac aacggggctt caaaataatt ttcttgggga ggttcaagac
                                                                        120
gcttcactgc ttgaaactta aatggatgtg ggacanaatt ttctgtaatg accctgaggg
                                                                        180
cattacagac gggactctgg gaggaaggat aaacagaaag gggacaaagg ctaatcccaa
                                                                        240
aacatcaaag aaaggaaggt ggcgtcatac ctcccagcct acacagttct ccagggctct
                                                                        300
cctcatccct ggaggacgac agtggaggaa caactgacca tgtccccagg ctcctgtgtg
                                                                        360
ctggctcctg gtcttcagcc cccagctctg gaagcccacc ctctgctgat cctgcgtggc
                                                                        420
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```
ccacacteet tgaacacaca tecceaggtt atatteetgg acatggetga aceteetatt
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cctacttccg agatgccttg ctcctgcag cctgtcaaaa tcccactcac cctccaaacc
                                                                        540
acggcatggg aagcctttct gacttgcctg attactccag catcttggaa caatccctga
                                                                        600
ttccccactc cttagaggca agatagggtg gttaagagta gggctggacc acttggagcc
                                                                        660
aggetgetgg etteaaattn tggeteattt acgagetatg ggacettggg caagtnatet
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tcacttctat gggcntcatt ttgttctacc tgcaaaatgg gggataataa tagt
                                                                        774
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      <211> 124
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(124)
      <223> n = A,T,C or G
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                                                                         60
ttgcaantat anaaatgtgt cataaattat aatgttcctt aattacagct caacgcaact
                                                                        120
tggt
                                                                        124
      <210> 49
      <211> 147
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(147)
      <223> n = A, T, C or G
      <400> 49
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                                                                        60
tgtggctaca ggtggtgtct gactgcatna aaaanttttt tacgggtgat tgcaaaaatt
                                                                       120
ttagggcacc catatcccaa qcantqt
                                                                       147
      <210> 50
      <211> 107
      <212> DNA
      <213> Homo sapien
      <400> 50
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                                                                        60
atggtttgag gttaggagga gttaggcata tgttttggga gaggggt
                                                                       107
      <210> 51
      <211> 204
     <212> DNA
     <213> Homo sapien
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<212> DNA

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<400> 51
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cgggaaggaa aggcagagaa gtgacaccgt cagggggaaa tgacagaaag gaaaatcaag
                                                                        120
gccttgcaag gtcagaaagg ggactcaggg cttccaccac agccctgccc cacttggcca
                                                                        180
cctccctttt gggaccagca atgt
                                                                        204
      <210> 52
      <211> 491
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(491)
      <223> n = A, T, C \text{ or } G
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                                                                         60
gggtattttc caaaagacta aagagataac tcaggtaaaa agttagaaat gtataaaaca
                                                                        120
ccatcagaca ggtttttaaa aaacaacata ttacaaaatt agacaatcat ccttaaaaaa
                                                                        180
aaaacttctt gtatcaattt cttttgttca aaatgactga cttaantatt tttaaatatt
                                                                        240
tcanaaacac ttcctcaaaa attttcaana tggtagcttt canatgtncc ctcagtccca
                                                                        300
atgttgctca gataaataaa tctcgtgaga acttaccacc caccacaaqc tttctqqqqc
                                                                        360
atgcaacagt gtcttttctt tnctttttct ttttttttt ttacaqqcac aqaaactcat
                                                                        420
caattttatt tggataacaa agggtctcca aattatattg aaaaataaat ccaagttaat
                                                                        480
atcactcttg t
                                                                        491
      <210> 53
      <211> 484
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(484)
      <223> n = A, T, C \text{ or } G
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gtattaacag ttgctgaagt ttggtatttt tatgcagcat tttctttttg ctttgataac
                                                                        120
actacagaac ccttaaggac actgaaaatt agtaagtaaa gttcagaaac attaqctqct
                                                                        180
caatcaaatc tctacataac actatagtaa ttaaaacgtt aaaaaaaagt gttgaaatct
                                                                        240
gcactagtat anaccgctcc tgtcaggata anactgcttt ggaacagaaa gggaaaaanc
                                                                        300
agetttgant ttetttgtge tgatangagg aaaggetgaa ttacettgtt geeteteeet
                                                                        360
aatgattggc aggtcnggta aatnccaaaa catattccaa ctcaacactt cttttccncq
                                                                        420
tancttgant ctgtgtattc caggancagg cggatggaat gggccagccc ncqqatqttc
                                                                        480
cant
                                                                        484
      <210> 54
      <211> 151
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## <213> Homo sapien <400> 54 actaaacctc gtgcttgtga actccataca gaaaacggtg ccatccctga acacggctgg 60 ccactgggta tactgctgac aaccgcaaca acaaaaacac aaatccttgg cactggctag 120 tctatgtcct ctcaagtgcc tttttgtttg t 151 <210> 55 <211> 91 <212> DNA <213> Homo sapien <400> 55 acctggcttg tctccgggtg gttcccggcg cccccacgg tccccagaac ggacactttc 60 gccctccagt ggatactcga gccaaagtgg t 91 <210> 56 <211> 133 <212> DNA <213> Homo sapien <400> 56 ggcggatgtg cgttggttat atacaaatat gtcattttat gtaagggact tgagtatact 60 tggatttttg gtatctgtgg gttgggggga cggtccagga accaataccc catggatacc 120 aagggacaac tgt 133 <210> 57 <211> 147 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1)...(147) <223> n = A, T, C or G<400> 57 actetggaga acctgageeg etgeteegee tetgggatga ggtgatgean gengtggege 60 gactgggagc tgagcccttc cctttgcgcc tgcctcagag gattgttgcc gacntqcana 120 tctcantggg ctggatncat gcagggt 147 <210> 58 <211> 198 <212> DNA <213> Homo sapien <220> <221> misc\_feature <222> (1)...(198) <223> n = A, T, C or G

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atttaccaat gagttacctt gtaaatgaga agtcatgata			180
ttgacttcta agtttggt			198
<210> 59			
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<212> DNA			
<213> Homo sapien			
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ccattgaaaa ttatcattaa tgattttaaa tgacaagtta cacctgtgct agcttgctaa aatgggagtt aactctagag			120 180
tacagtcaat aaatgacaaa gccagggcct acaggtggtt			240
cagaaggaat ctattttatc acatggatct ccgtctgtgc	tcaaaatacc	taatgatatt	300
tttcgtcttt attggacttc tttgaagagt			330
<210> 60			
<211> 175			
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(213) Homo Sapien			
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gtegtggget cetteetett cateeteate cagetggtge teetggaace ageggtgget gggcaaggee gaggagtgeg			175
<210> 61			
<211> 154 <212> DNA			
<213> Homo sapien			
.400. 61			
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ggttgttgct cttcaacagt atcctcccct ttccggatct			120
tggactgcac agccccgggg ctccacattg ctgt			154
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<212> DNA			
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cgctcgagcc ctatagtgag tcgtattaga			30
<210> 63			
<211> 89			
<212> DNA			
<213> Homo sapien			

<400> 63 acaagtcatt tcagcaccct ttgctcttca aaactgacca tcttttatat ttaatgctt ctgtatgaat aaaaatggtt atgtcaagt	c 60 89
<210> 64 <211> 97 <212> DNA <213> Homo sapien	
<400> 64 accggagtaa ctgagtcggg acgctgaatc tgaatccacc aataaataaa ggttctgca aatcagtgca tccaggattg gtccttggat ctggggt	g 60 97
<210> 65 <211> 377 <212> DNA <213> Homo sapien	
<220> <221> misc_feature <222> (1)(377) <223> n = A,T,C or G	
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<210> 66 <211> 305 <212> DNA <213> Homo sapien	
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<210> 67 <211> 385 <212> DNA <213> Homo sapien	

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                                                                       120
cccttttaaa aaaggggact tgcttaaaaa agaagtctag ccacgattgt gtagagcagc
                                                                       180
tgtgctgtgc tggagattca cttttgagag agttctcctc tgagacctga tctttagagg
                                                                       240
ctgggcagtc ttgcacatga gatggggctg gtctgatctc agcactcctt agtctgcttg
                                                                       300
ceteteccag ggeeccagee tggeeacace tgettacagg geacteteag atgeecatae
                                                                       360
catagtttct gtgctagtgg accgt
                                                                       385
      <210> 68
      <211> 73
      <212> DNA
      <213> Homo sapien
      <400> 68
acttaaccag atatattttt accccagatg gggatattct ttgtaaaaaa tgaaaataaa
                                                                        60
gtttttttaa tgg
                                                                        73
      <210> 69
      <211> 536
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(536)
      <223> n = A, T, C or G
      <400> 69
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                                                                        60
tccagctttg tgctctgcct ctgaggagac catggcccag catctgagta ccctgctgct
                                                                       120
cctgctggcc accctagctg tggccctggc ctggagcccc aaggaggagg ataggataat
                                                                       180
ecegggtgge atetataacg cagaceteaa tgatgagtgg gtacagegtg ceetteaett
                                                                       240
cgccatcagc gagtataaca aggccaccaa agatgactac tacagacgtc cgctgcgggt
                                                                       300
actaagagcc aggcaacaga ccgttggggg ggtgaattac ttcttcgacg tagaggtggg
                                                                       360
ccgaaccata tgtaccaagt cccagcccaa cttggacacc tgtgccttcc atgaacagcc
                                                                       420
agaactgcag aagaaacagt tgtgctcttt cgagatctac gaagttccct ggggagaaca
                                                                       480
gaangteeet gggtgaaate caggtgteaa gaaateetan ggatetgttg eeagge
                                                                       536
      <210> 70
      <211> 477
      <212> DNA
      <213> Homo sapien
     <400> 70
atgaccccta acaggggccc tctcagccct cctaatgacc tccggcctag ccatgtgatt
                                                                        60
tcacttccac tccataacgc tcctcatact aggcctacta accaacacac taaccatata
                                                                       120
ccaatgatgg cgcgatgtaa cacgagaaag cacataccaa ggccaccaca caccacctgt
                                                                       180
ccaaaaaggc cttcgatacg ggataatcct atttattacc tcagaagttt ttttcttcgc
                                                                       240
agggattttt ctgagcettt taccactcca geetageeee tacceecaa ctaggaggge
                                                                       300
actggccccc aacaggcatc accccgctaa atcccctaga agtcccactc ctaaacacat
                                                                       360
ccgtattact cgcatcagga gtatcaatca cctgagctca ccatagtcta atagaaaaca
                                                                       420
```

```
accgaaacca aattattcaa agcactgctt attacaattt tactgggtct ctatttt
                                                                       477
      <210> 71
      <211> 533
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(533)
      <223> n = A, T, C or G
      <400> 71
agagetatag gtacagtgtg ateteagett tgeaaacaca ttttetacat agatagtact
                                                                        60
aggtattaat agatatgtaa agaaagaaat cacaccatta ataatggtaa gattggttta
                                                                       120
tgtgatttta gtggtatttt tggcaccctt atatatgttt tccaaacttt cagcagtgat
                                                                       180
attatttcca taacttaaaa agtgagtttg aaaaagaaaa tctccagcaa gcatctcatt
                                                                       240
taaataaagg tttgtcatct ttaaaaatac agcaatatgt gactttttaa aaaagctgtc
                                                                       300
aaataggtgt gaccctacta ataattatta gaaatacatt taaaaaacatc gagtacctca
                                                                       360
agtcagtttg ccttgaaaaa tatcaaatat aactcttaga gaaatgtaca taaaagaatg
                                                                       420
cttcgtaatt ttggagtang aggttccctc ctcaattttg tatttttaaa aagtacatgg
                                                                       480
taaaaaaaaa aattcacaac agtatataag gctgtaaaat gaagaattct gcc
                                                                       533
      <210> 72
      <211> 511
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(511)
      <223> n = A, T, C or G
      <400> 72
tattacggaa aaacacacca cataattcaa ctancaaaga anactgcttc agggcgtgta
                                                                        60
aaatgaaagg cttccaggca gttatctgat taaagaacac taaaagaggg acaaggctaa
                                                                       120
aagccgcagg atgtctacac tatancaggc gctatttggg ttggctggag gagctgtgga
                                                                       180
aaacatggan agattggtgc tgganatcgc cgtggctatt cctcattgtt attacanagt
                                                                       240
gaggttctct gtgtgcccac tggtttgaaa accgttctnc aataatgata gaatagtaca
                                                                       300
cacatgagaa ctgaaatggc ccaaacccag aaagaaagcc caactagatc ctcagaanac
                                                                       360
gcttctaggg acaataaccg atgaagaaaa gatggcctcc ttgtgccccc gtctgttatg
                                                                       420
atttctctcc attgcagcna naaacccqtt cttctaagca aacncaqqtg atgatqqcna
                                                                       480
aaatacaccc cctcttgaag naccnggagg a
                                                                       511
      <210> 73
      <211> 499
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
```

```
<222> (1)...(499)
      <223> n = A, T, C \text{ or } G
      <400> 73
cagtgccagc actggtgcca gtaccagtac caataacagt gccagtgcca gtgccagcac
                                                                       60
cagtggtggc ttcagtgctg gtgccagcct gaccgccact ctcacatttg ggctcttcgc
                                                                      120
tggccttggt ggagctggtg ccagcaccag tggcagctct ggtgcctgtg gtttctccta
                                                                      180
caagtgagat tttagatatt gttaatcctg ccagtctttc tcttcaagcc agggtgcatc
                                                                      240
ctcagaaacc tactcaacac agcactctag gcagccacta tcaatcaatt gaagttgaca
                                                                      300
360
antctagagg gcccgtttaa acccgctgat cagcctcgac tgtgccttct anttgccagc
                                                                      420
catctgttgt ttgcccctcc cccgntgcct tccttgaccc tggaaagtgc cactcccact
                                                                      480
gtcctttcct aantaaaat
                                                                      499
      <210> 74
      <211> 537
      <212> DNA
      <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(537)
     <223> n = A, T, C \text{ or } G
     <400> 74
tttcatagga gaacacactg aggagatact tgaagaattt ggattcagcc gcgaagagat
                                                                       60
ttatcagctt aactcagata aaatcattga aagtaataag gtaaaagcta gtctctaact
                                                                      120
tccaggccca cggctcaagt gaatttgaat actgcattta cagtgtagag taacacataa
                                                                      180
cattgtatgc atggaaacat ggaggaacag tattacagtg tcctaccact ctaatcaaga
                                                                      240
aaagaattac agactctgat tctacagtga tgattgaatt ctaaaaaatgg taatcattag
                                                                      300
ggcttttgat ttataanact ttgggtactt atactaaatt atggtagtta tactgccttc
                                                                      360
cagtttgctt gatatatttg ttgatattaa gattcttgac ttatattttg aatgggttct
                                                                      420
actgaaaaan gaatgatata ttcttgaaga catcgatata catttattta cactcttgat
                                                                      480
tctacaatgt agaaaatgaa ggaaatgccc caaattgtat ggtgataaaa gtcccgt
                                                                      537
      <210> 75
      <211> 467
      <212> DNA
     <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1)...(467)
     \langle 223 \rangle n = A,T,C or G
     <400> 75
caaanacaat tgttcaaaag atgcaaatga tacactactg ctgcagctca caaacacctc
                                                                       60
tgcatattac acgtacctcc tcctgctcct caagtagtgt ggtctatttt gccatcatca
                                                                      120
cctgctgtct gcttagaaga acggctttct gctgcaangg agagaaatca taacagacgg
                                                                      180
tggcacaagg aggccatctt ttcctcatcg gttattgtcc ctagaagcgt cttctgagga
                                                                      240
tctagttggg ctttctttct gggtttgggc catttcantt ctcatgtgtg tactattcta
                                                                      300
```

```
tcattattgt ataacggttt tcaaaccngt gggcacncag agaacctcac tctgtaataa
                                                                        360
caatgaggaa tagccacggt gatctccagc accaaatctc tccatgttnt tccagagctc
                                                                        420
ctccagccaa cccaaatagc cgctgctatn gtgtagaaca tccctgn
                                                                        467
      <210> 76
      <211> 400
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(400)
      <223> n = A, T, C \text{ or } G
      <400> 76
aagetgacag cattegggee gagatgtete geteegtgge ettagetgtg eteqeqetae
                                                                         60
tetetettte tggcetggag getatecage gtaetecaaa gatteaggtt taeteaegte
                                                                        120
atccagcaga gaatggaaag tcaaatttcc tgaattgcta tgtgtctggg tttcatccat
                                                                        180
ccgacattga agttgactta ctgaagaatg gagagagaat tgaaaaagtg gagcattcag
                                                                        240
acttgtcttt cagcaaggac tggtctttct atctcttgta ctacactgaa ttcaccccca
                                                                        300
ctgaaaaaga tgagtatgcc tgccgtgtga accatgtgac tttgtcacag cccaagatng
                                                                        360
ttnagtggga tcganacatg taagcagcan catgggaggt
                                                                        400
      <210> 77
      <211> 248
      <212> DNA
      <213> Homo sapien
      <400> 77
ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct
                                                                         60
ccagctgccc cggcgggga tgcgaggctc ggagcaccct tgcccggctg tgattgctgc
                                                                        120
caggeactgt teateteage ttttetgtee etttgeteee ggeaageget tetgetgaaa
                                                                        180
gttcatatct ggagcctgat gtcttaacga ataaaggtcc catgctccac ccgaaaaaaa
                                                                        240
aaaaaaaa
                                                                        248
      <210> 78
      <211> 201
      <212> DNA
      <213> Homo sapien
      <400> 78
actagtccag tgtggtggaa ttccattgtg ttgggcccaa cacaatggct acctttaaca
                                                                        60
teacceagae ecegecetge eegtgeecea egetgetget aacgacagta tgatgettae
                                                                        120
totgotacto ggaaactatt tttatgtaat taatgtatgo tttottgttt ataaatgoot
                                                                        180
gatttaaaaa aaaaaaaaa a
                                                                        201
      <210> 79
      <211> 552
      <212> DNA
      <213> Homo sapien
```

```
<220>
      <221> misc feature
      <222> (1)...(552)
      <223> n = A, T, C \text{ or } G
      <400> 79
tccttttgtt aggtttttga gacaacccta gacctaaact gtgtcacaga cttctgaatg
                                                                         60
tttaggcagt gctagtaatt tcctcgtaat gattctgtta ttactttcct attctttatt
                                                                        120
cctctttctt ctgaagatta atgaagttga aaattgaggt ggataaatac aaaaaggtag
                                                                        180
tgtgatagta taagtatcta agtgcagatg aaagtgtgtt atatatatcc attcaaaatt
                                                                        240
atgcaagtta gtaattactc agggttaact aaattacttt aatatgctgt tgaacctact
                                                                        300
ctgttccttg gctagaaaaa attataaaca ggactttgtt agtttgggaa gccaaattga
                                                                        360
taatattota tgttotaaaa gttgggotat acataaanta tnaagaaata tggaatttta
                                                                        420
ttcccaggaa tatggggttc atttatgaat antacccggg anagaagttt tgantnaaac
                                                                        480
cngttttggt taatacgtta atatgtcctn aatnaacaag gcntgactta tttccaaaaa
                                                                        540
aaaaaaaaa aa
                                                                        552
      <210> 80
      <211> 476
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(476)
      <223> n = A, T, C or G
      <400> 80
acagggattt gagatgctaa ggccccagag atcgtttgat ccaaccctct tattttcaga
                                                                         60
ggggaaaatg gggcctagaa gttacagagc atctagctgg tgcqctqqca cccctqqcct
                                                                        120
cacacagact cccgagtagc tgggactaca ggcacacagt cactgaagca ggccctgttt
                                                                        180
gcaattcacg ttgccacctc caacttaaac attcttcata tgtgatgtcc ttagtcacta
                                                                        240
aggttaaact ttcccaccca gaaaaggcaa cttagataaa atcttagagt actttcatac
                                                                        300
tottetaagt cotottecag cotoactitg agtoctcott gggggttgat aggaaninto
                                                                        360
tcttggcttt ctcaataaaa tctctatcca tctcatgttt aatttggtac gcntaaaaat
                                                                        420
gctgaaaaaa ttaaaatgtt ctggtttcnc tttaaaaaaa aaaaaaaaa aaaaaa
                                                                        476
      <210> 81
      <211> 232
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(232)
      <223> n = A, T, C \text{ or } G
      <400> 81
ttttttttttt tatgcenten etgtggngtt attgttgetg ecaceetgga ggageecagt
                                                                         60
ttcttctgta tctttctttt ctgggggatc ttcctggctc tgcccctcca ttcccagcct
                                                                        120
ctcatcccca tcttgcactt ttgctagggt tggaggcgct ttcctggtag cccctcagag
                                                                        180
```

```
actcagtcag cgggaataag tcctaggggt ggggggtgtg gcaagccggc ct
                                                                       232
      <210> 82
      <211> 383
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(383)
      <223> n = A, T, C or G
      <400> 82
aggcgggagc agaagctaaa gccaaagccc aagaagagtg gcagtgccag cactggtgcc
                                                                        60
agtaccagta ccaataacat gccagtgcca gtgccagcac cagtggtggc ttcagtgctg
                                                                       120
gtgccagcct gaccgccact ctcacatttg ggctcttcgc tggccttggt ggagctggtg
                                                                       180
ccagcaccag tggcagetet ggtgeetgtg gttteteeta caaqtqaqat tttaqatatt
                                                                       240
gttaatcctg ccagtctttc tcttcaagcc agggtgcatc ctcagaaacc tactcaacac
                                                                       300
agcactetng geagecacta teaateaatt gaagttgaca etetqeatta aatetatttq
                                                                       360
ccatttcaaa aaaaaaaaaa aaa
                                                                       383
      <210> 83
      <211> 494
      <212> DNA
      <213> Homo sapien
      <220>
     <221> misc feature
      <222> (1)...(494)
      <223> n = A,T,C or G
      <400> 83
accgaattgg gaccgctggc ttataagcga tcatgtcctc cagtattacc tcaacgagca
                                                                        60
gggagatega gtetataege tgaagaaatt tgaceegatg ggacaacaga cetgeteage
                                                                       120
ccatcctgct cggttctccc cagatgacaa atactctcga caccqaatca ccatcaaqaa
                                                                       180
acgcttcaag gtgctcatga cccagcaacc gcgccctgtc ctctgagggt ccttaaactg
                                                                       240
atgtetttte tgecacetgt taecectegg agaeteegta accaaactet teggactgtg
                                                                       300
agccctgatg cctttttgcc agccatactc tttggcntcc agtctctcgt ggcgattgat
                                                                       360
tatgcttgtg tgaggcaatc atggtggcat cacccatnaa gggaacacat ttqanttttt
                                                                       420
tttcncatat tttaaattac naccagaata nttcagaata aatgaattga aaaactctta
                                                                       480
aaaaaaaaa aaaa
                                                                       494
      <210> 84
      <211> 380
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(380)
      <223> n = A, T, C or G
```

```
<400> 84
gctggtagcc tatggcgtgg ccacggangg gctcctgagg cacgggacag tgacttccca
                                                                        60
agtatectge geogegtett etacegteee tacetgeaga tettegggea gatteeecag
                                                                        120
gaggacatgg acgtggccct catggagcac agcaactgct cgtcggagcc cggcttctgg
                                                                        180
gcacaccete etggggeeca ggegggeace tgegtetece agtatgeeaa etggetggtg
                                                                        240
gtgctgctcc tcgtcatctt cctgctcgtg gccaacatcc tgctggtcac ttgctcattg
                                                                        300
ccatgttcag ttacacattc ggcaaagtac agggcaacag cnatctctac tgggaaggcc
                                                                        360
agcgttnccg cctcatccgg
                                                                        380
      <210> 85
      <211> 481
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(481)
      <223> n = A,T,C or G
      <400> 85
gagttagete etecacaace ttgatgaggt egtetgeagt ggeetetege tteatacege
                                                                        60
tnccatcgtc atactgtagg tttgccacca cctcctgcat cttggggcgg ctaatatcca
                                                                        120
ggaaactete aatcaagtea eegtenatna aacetgtgge tggttetgte tteegetegg
                                                                        180
tgtgaaagga tctccagaag gagtgctcga tcttccccac acttttgatg actttattga
                                                                        240
gtcgattctg catgtccagc aggaggttgt accagetete tgacagtgag gtcaccagec
                                                                        300
ctatcatgcc nttgaacgtg ccgaagaaca ccgagccttg tgtggggggt gnagtctcac
                                                                        360
ccagattctg cattaccaga nagccgtggc aaaaganatt gacaactcgc ccaggnngaa
                                                                        420
aaagaacacc teetggaagt getngeeget cetegteent tggtggnnge gentneettt
                                                                        480
                                                                        481
      <210> 86
      <211> 472
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(472)
      <223> n = A, T, C \text{ or } G
      <400> 86
aacatcttcc tgtataatgc tgtgtaatat cgatccgatn ttgtctgctg agaattcatt
                                                                        60
acttggaaaa gcaacttnaa gcctggacac tggtattaaa attcacaata tgcaacactt
                                                                       120
taaacagtgt gtcaatctgc tcccttactt tgtcatcacc agtctgggaa taagggtatg
                                                                       180
ccctattcac acctgttaaa agggcgctaa gcatttttga ttcaacatct ttttttttga
                                                                       240
cacaagtccg aaaaaagcaa aagtaaacag ttnttaattt gttagccaat tcactttctt
                                                                       300
catgggacag agccatttga tttaaaaagc aaattgcata atattgagct ttgggagctg
                                                                       360
atatntgagc ggaagantag cetttetaet teaccagaca caacteettt catattggga
                                                                       420
tgttnacnaa agttatgtct cttacagatg ggatgctttt gtggcaattc tg
                                                                       472
```

```
<210> 87
      <211> 413
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(413)
      <223> n = A, T, C \text{ or } G
      <400> 87
agaaaccagt atctctnaaa acaacctctc ataccttgtg gacctaattt tgtgtgcgtg
                                                                         60
tgtgtgtgcg cgcatattat atagacaggc acatcttttt tacttttgta aaagcttatg
                                                                         120
cctctttggt atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct
                                                                         180
ttgtcttctg tgtaaatggt actagagaaa acacctatnt tatgagtcaa tctagttngt
                                                                         240
tttattcgac atgaaggaaa tttccagatn acaacactna caaactctcc cttgactagg
                                                                         300
ggggacaaag aaaagcanaa ctgaacatna gaaacaattn cctggtgaga aattncataa
                                                                         360
acagaaattg ggtngtatat tgaaananng catcattnaa acgttttttt ttt
                                                                         413
      <210> 88
      <211> 448
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(448)
      <223> n = A, T, C \text{ or } G
      <400> 88
egeagegggt cetetetate tageteeage etetegeetg ecceaeteee egegteeege
                                                                         60
gtcctagecn accatggccg ggcccctgcg cgccccgctg ctcctgctgg ccatcctggc
                                                                        120
cgtggccctg gccgtgagcc ccgcggccgg ctccagtccc ggcaagccgc cgcgcctggt
                                                                        180
gggaggeeca tggaceeege gtggaagaag aaggtgtgeg gegtgeaetg gaetttgeeg
                                                                        240
teggenanta caacaaacce geaacnactt ttacenagen egegetgeag gttgtgeege
                                                                        300
cccaancaaa ttgttactng gggtaantaa ttcttggaag ttgaacctgg gccaaacnng
                                                                        360
tttaccagaa ccnagccaat tngaacaatt ncccctccat aacagcccct tttaaaaagg
                                                                        420
gaancantcc tgntcttttc caaatttt
                                                                        448
      <210> 89
      <211> 463
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(463)
      <223> n = A, T, C or G
      <400> 89
gaattttgtg cactggccac tgtgatggaa ccattgggcc aggatgcttt gagtttatca
                                                                         60
```

```
gtagtgattc tgccaaagtt ggtgttgtaa catgagtatg taaaatgtca aaaaattagc
                                                                        120
agaggtctag gtctgcatat cagcagacag tttgtccgtg tattttgtag ccttgaagtt
                                                                        180
ctcagtgaca agttnnttct gatgcgaagt tctnattcca gtgttttagt cctttgcatc
                                                                        240
tttnatgttn agacttgcct ctntnaaatt gcttttgtnt tctgcaggta ctatctgtgg
                                                                        300
tttaacaaaa tagaannact tctctqcttn qaanatttqa atatcttaca tctnaaaatn
                                                                        360
aattetetee eeatannaaa acceangeee ttggganaat ttgaaaaang gnteettenn
                                                                        420
aattennana antteagntn teatacaaca naaenggane eec
                                                                        463
      <210> 90
      <211> 400
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(400)
      <223> n = A, T, C \text{ or } G
      <400> 90
agggattgaa ggtctnttnt actgtcggac tgttcancca ccaactctac aagttgctgt
                                                                         60
cttccactca ctgtctgtaa gcntnttaac ccagactgta tcttcataaa tagaacaaat
                                                                        120
tcttcaccag tcacatcttc taggaccttt ttggattcag ttagtataag ctcttccact
                                                                        180
tcctttgtta agacttcatc tggtaaagtc ttaagttttg tagaaaggaa tttaattgct
                                                                        240
cgttctctaa caatgtcctc tccttgaagt atttggctga acaacccacc tnaaqtccct
                                                                        300
ttgtgcatcc attttaaata tacttaatag ggcattggtn cactaggtta aattctgcaa
                                                                        360
gagtcatctg tctgcaaaag ttgcgttagt atatctgcca
                                                                        400
      <210> 91
      <211> 480
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(480)
      <223> n = A, T, C \text{ or } G
      <400> 91
gagctcggat ccaataatct ttgtctgagg gcagcacaca tatncagtgc catggnaact
                                                                        60
ggtctacccc acatgggagc agcatgccgt agntatataa ggtcattccc tgagtcagac
                                                                        120
atgeetettt gaetaeegtg tgeeagtget ggtgattete acacacetee nneegetett
                                                                        180
tgtggaaaaa ctggcacttg nctggaacta gcaagacatc acttacaaat tcacccacga
                                                                        240
gacacttgaa aggtgtaaca aagcgactct tqcattqctt tttqtccctc cqqcaccaqt
                                                                        300
tgtcaatact aaccegetgg tttgcctcca tcacatttgt gatctgtage tctggataca
                                                                        360
totoctgaca gtactgaaga acttottott ttqtttcaaa aqcaactott qqtqcctqtt
                                                                        420
ngatcaggtt cccatttccc agtccgaatg ttcacatggc atainttact tcccacaaaa
                                                                        480
      <210> 92
      <211> 477
      <212> DNA
      <213> Homo sapien
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<220>
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      <222> (1)...(477)
      \langle 223 \rangle n = A,T,C or G
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                                                                          60
ggtcccgctg tagccccagc gactctccac ctgctggaag cggttgatgc tgcactcctt
                                                                         120
cccacgcagg cagcagcggg gccggtcaat gaactccact cgtggcttgg ggttgacggt
                                                                         180
taantgcagg aagaggctga ccacctogcg gtccaccagg atgcccgact gtgcgggacc
                                                                         240
tgcagcgaaa ctcctcgatg gtcatgagcg ggaagcgaat gangcccagg gccttgccca
                                                                         300
gaacetteeg cetgttetet ggegteacet geagetgetg cegetnacae teggeetegg
                                                                         360
accageggae aaaeggegtt gaacageege accteaegga tgeecantgt gtegegetee
                                                                         420
aggaacggcn ccagcgtgtc caggtcaatg tcggtgaanc ctccgcgggt aatggcg
                                                                         477
      <210> 93
      <211> 377
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(377)
      \langle 223 \rangle n = A,T,C or G
      <400> 93
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                                                                         60
agteegagea geeceagace getgeegeee gaagetaage etgeetetgg cetteecete
                                                                         120
cgcctcaatg cagaaccant agtgggagca ctgtgtttag agttaagagt gaacactgtn
                                                                         180
tgattttact tgggaatttc ctctgttata tagcttttcc caatgctaat ttccaaacaa
                                                                         240
caacaacaaa ataacatgtt tgcctgttna gttgtataaa agtangtgat tctgtatnta
                                                                         300
aagaaaatat tactgttaca tatactgctt gcaanttctg tatttattgg tnctctggaa
                                                                         360
ataaatatat tattaaa
                                                                         377
      <210> 94
      <211> 495
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(495)
      <223> n = A, T, C \text{ or } G
      <400> 94
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                                                                         60
egagetgang cagattteec acagtgacce cagageeetg ggetatagte tetgacceet
                                                                        120
ccaaggaaag accacettet ggggacatgg getggaggge aggacetaga ggcaceaagg
                                                                        180
gaaggcccca ttccggggct gttccccgag gaggaaggga aggggctctg tgtgccccc
                                                                         240
acgaggaana ggccctgant cctgggatca nacacccctt cacgtgtatc cccacacaaa
                                                                        300
```

```
tgcaagetca ccaaggtece eteteagtee etteectaca ecetgaaegg neactggeee
                                                                       360
acacccaccc agancancca cccqccatqq qqaatqtnct caaqqaatcq cnqqqcaacq
                                                                       420
tggactetng tecennaagg gggeagaate tecaatagan gganngaace ettgetnana
                                                                       480
aaaaaaana aaaaa
                                                                       495
      <210> 95
      <211> 472
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
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      <223> n = A, T, C or G
      <400> 95
ggttacttgg tttcattgcc accacttagt ggatgtcatt tagaaccatt ttgtctgctc
                                                                        60
cctctggaag ccttgcgcag agcggacttt gtaattgttg gagaataact gctgaatttt
                                                                       120
tagctgtttt gagttgattc gcaccactgc accacaactc aatatgaaaa ctatttnact
                                                                       180
tatttattat cttgtgaaaa gtatacaatg aaaattttgt tcatactgta tttatcaagt
                                                                       240
atgatgaaaa gcaatagata tatattcttt tattatgttn aattatgatt gccattatta
                                                                       300
atcggcaaaa tgtggagtgt atgttctttt cacagtaata tatgcctttt gtaacttcac
                                                                       360
ttggttattt tattgtaaat gaattacaaa attcttaatt taagaaaatg gtangttata
                                                                       420
tttanttcan taatttcttt ccttgtttac gttaattttg aaaagaatgc at
                                                                       472
      <210> 96
      <211> 476
      <212> DNA
      <213> Homo sapien
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      <221> misc feature
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      <223> n = A, T, C or G
      <400> 96
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gtggtgaaat ttcaaaatta tatgtaactt ctactagttt tactttctcc cccaagtctt
                                                                       120
ttttaactca tgatttttac acacacaatc cagaacttat tatatagcct ctaagtcttt
                                                                       180
attetteaca gtagatgatg aaagagteet ecagtgtett gngcanaatg ttetagntat
                                                                       240
agctggatac atacngtggg agttctataa actcatacct cagtgggact naaccaaaat
                                                                       300
tgtgttagtc tcaattccta ccacactgag ggagcctccc aaatcactat attcttatct
                                                                       360
gcaggtactc ctccagaaaa acngacaggg caggcttgca tgaaaaagtn acatctgcgt
                                                                       420
tacaaagtct atcttcctca nangtctgtn aaggaacaat ttaatcttct agcttt
                                                                       476
      <210> 97
      <211> 479
      <212> DNA
      <213> Homo sapien
      <220>
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<221> misc feature
      <222> (1)...(479)
      <223> n = A, T, C \text{ or } G
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aaataatgct gcaaacttaa tgttcttatg caaaatggaa cgctaatgaa acacagctta
                                                                       120
caatcgcaaa tcaaaactca caagtgctca tctgttgtag atttagtgta ataagactta
                                                                       180
gattgtgctc cttcggatat gattgtttct canatcttgg gcaatnttcc ttagtcaaat
                                                                       240
caggetacta gaattetgtt attggatatn tgagageatg aaatttttaa naatacaett
                                                                       300
gtgattatna aattaatcac aaatttcact tatacctgct atcagcagct agaaaaacat
                                                                       360
ntnnttttta natcaaagta ttttgtgttt ggaantgtnn aaatgaaatc tgaatgtggg
                                                                       420
ttenatetta tttttteeen gaenaetant tnetttttta gggnetatte tganecate
                                                                       479
      <210> 98
      <211> 461
      <212> DNA
      <213> Homo sapien
      <400> 98
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tgctagttcc tgtcatctat tcgctactaa atgcagactg gaggggacca aaaaggggca
                                                                       120
tcaactccag ctggattatt ttggagcctg caaatctatt cctacttgta cggactttga
                                                                       180
agtgattcag tttcctctac ggatgagaga ctggctcaag aatatcctca tgcagcttta
                                                                       240
tgaagccact ctgaacacgc tggttatcta gatgagaaca gagaaataaa gtcagaaaat
                                                                       300
ttacctggag aaaagagget ttggetgggg accateceat tgaacettet ettaaggaet
                                                                       360
ttaagaaaaa ctaccacatg ttgtgtatcc tggtgccggc cgtttatgaa ctgaccaccc
                                                                       420
tttggaataa tcttgacgct cctgaacttg ctcctctgcg a
                                                                       461
      <210> 99
      <211> 171
      <212> DNA
      <213> Homo sapien
      <400> 99
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                                                                        60
eggegeetet gegggeeega ggaggagegg etggegggtg gggggagtgt gacceaecet
                                                                       120
cggtgagaaa agccttctct agcgatctga gaggcgtgcc ttgggggtac c
                                                                       171
      <210> 100
      <211> 269
      <212> DNA
      <213> Homo sapien
      <400> 100
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cgactgcgac gacggcggcg gcgacagtcg caggtgcagc gcgggcgcct ggggtcttgc
                                                                       120
aaggetgage tgaegeegea gaggtegtgt caegteeeae gaeettgaeg eegtegggga
                                                                       180
cageeggaac agageeeggt gaagegggag geetegggga geeeeteggg aagggeggee
                                                                       240
cgagagatac gcaggtgcag gtggccgcc
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                                                                     120
ttgattggtt tgtctttatg ggggcggggt ggggtagggg aaacgaagca aataacatgg
                                                                     180
agtgggtgca ccctccctgt agaacctggt tacaaagctt ggggcagttc acctgqtctg
                                                                     240
tgaccgtcat tttcttgaca tcaatgttat tagaagtcag gatatctttt agagagtcca
                                                                     300
ctgttctgga gggagattag ggtttcttgc caaatccaac aaaatccact gaaaaaqttq
                                                                     360
gatgatcagt acgaataccg aggcatattc tcatatcggt ggcca
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     <211> 470
     <212> DNA
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tcaaaatcta aattattcaa attagccaaa tccttaccaa ataataccca aaaatcaaaa
                                                                    180
atatacttct ttcagcaaac ttgttacata aattaaaaaa atatatacgg ctggtgtttt
                                                                    240
caaagtacaa ttatcttaac actgcaaaca ttttaaggaa ctaaaataaa aaaaaacact
                                                                    300
ccgcaaaggt taaagggaac aacaaattct tttacaacac cattataaaa atcatatctc
                                                                    360
aaatettagg ggaatatata etteacaegg gatettaaet tttaeteaet ttgtttattt
                                                                    420
ttttaaacca ttgtttgggc ccaacacaat ggaatccccc ctggactagt
                                                                    470
     <210> 103
     <211> 581
     <212> DNA
     <213> Homo sapien
     <400> 103
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tacacatatt tattttataa ttggtattag atattcaaaa ggcagctttt aaaatcaaac
                                                                    120
taaatggaaa ctgccttaga tacataattc ttaggaatta gcttaaaatc tgcctaaagt
                                                                    180
gaaaatette tetagetett tigaetgiaa attittigaet etigtaaaac atccaaatte
                                                                    240
atttttcttg tctttaaaat tatctaatct ttccattttt tccctattcc aagtcaattt
                                                                    300
gcttctctag cctcatttcc tagctcttat ctactattag taagtggctt ttttcctaaa
                                                                    360
agggaaaaca ggaagagaaa tggcacacaa aacaaacatt ttatattcat atttctacct
                                                                    420
acgttaataa aatagcattt tgtgaagcca gctcaaaaga aggcttagat ccttttatgt
                                                                    480
ccattttagt cactaaacga tatcaaagtg ccagaatgca aaaggtttgt gaacatttat
                                                                    540
tcaaaagcta atataagata tttcacatac tcatctttct g
                                                                    581
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     <212> DNA
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                                                                     180
aggaaatctg ttcattcttc tcattcatat agttatatca agtactacct tgcatattga
                                                                     240
gaggtttttc ttctctattt acacatatat ttccatgtga atttgtatca aacctttatt
                                                                     300
ttcatgcaaa ctagaaaata atgtttcttt tgcataagag aagagaacaa tatagcatta
                                                                     360
caaaactgct caaattgttt gttaagttat ccattataat tagttggcag gagctaatac
                                                                     420
aaatcacatt tacgacagca ataataaaac tgaagtacca gttaaatatc caaaataatt
                                                                     480
aaaggaacat ttttagcctg ggtataatta gctaattcac tttacaagca tttattagaa
                                                                     540
tgaattcaca tgttattatt cctagcccaa cacaatgg
                                                                     578
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      <211> 538
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      <213> Homo sapien
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gaaaagtgcc ttacatttaa taaaagtttg tttctcaaag tgatcagagg aattagatat
                                                                     120
gtcttgaaca ccaatattaa tttgaggaaa atacaccaaa atacattaag taaattattt
                                                                     180
aagatcatag agcttgtaag tgaaaagata aaatttgacc tcagaaactc tgagcattaa
                                                                     240
aaatccacta ttagcaaata aattactatg gacttcttgc tttaattttg tgatgaatat
                                                                     300
ggggtgtcac tggtaaacca acacattctg aaggatacat tacttagtga tagattctta
                                                                     360
tgtactttgc taatacgtgg atatgagttg acaagtttct ctttcttcaa tcttttaagg
                                                                     420
ggcgagaaat gaggaagaaa agaaaaggat tacgcatact gttctttcta tggaaggatt
                                                                     480
agatatgttt cctttgccaa tattaaaaaa ataataatgt ttactactag tgaaaccc
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      <211> 473
      <212> DNA
      <213> Homo sapien
      <400> 106
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atttattagc tctgcaactt acatatttaa attaaagaaa cgttttagac aactgtacaa
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tttataaatg taaggtgcca ttattgagta atatatteet ecaagagtgg atgtgteeet
                                                                     180
teteccacea actaatgaae ageaacatta gtttaatttt attagtagat atacaetget
                                                                     240
gcaaacgcta attetettet ccatececat gtgatattgt gtatatgtgt gagttggtag
                                                                     300
aatgcatcac aatctacaat caacagcaag atgaagctag gctgggcttt cggtgaaaat
                                                                     360
agactgtgtc tgtctgaatc aaatgatctg acctatcctc ggtggcaaga actcttcgaa
                                                                     420
ccgcttcctc aaaggcgctg ccacatttgt ggctctttgc acttgtttca aaa
                                                                     473
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                                                                     120
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ccgctacgac gtgagccgct tgggccgggg caagcgctcg ctagtgctgg acctgaagca
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gccgcgggga gccgccgtgc tgcggcgtct gtgcaagcgg tcggatgtgc tgctggagcc
                                                                    240
cttccgccgc ggtgtcatgg agaaactcca gctgggccca gagattctgc agcgggaaaa
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tccaaggett atttatgcca ggctgagtgg atttggccag tcaggaaget tctgccggtt
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agctggccac gatatcaact atttggcttt gtcaggtgtt ctctcaaaaa ttgqcaqaaq
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tggtgagaat ccgtatgccc cgctgaatct cctggctgac tttqctqqtq qtqqccttat
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gtgtgcactg ggcattataa tggctctttt tgaccgcaca cgcactgaca aqqqtcaqqt
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gaaatcgagt ctgtgggaag cacctcgagg acagaacatg ttggatggtg gagcaccttt
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ctatacgact tacaggacag caqatgqqqa attcatqqct qttqqaqcaa taqaacccca
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gttctacgag ctgctgatca aaggacttgg actaaagtct gatgaacttc ccaatcagat
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                                                                    840
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cageegegaa gagatttate agettaaete agataaaate attgaaagta ataaggtaaa
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tagagtaaca cataacattg tatgcatgga aacatggagg aacagtatta cagtgtccta
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1620
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<400> 108

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Ala Pro Leu Asn Leu Leu Ala Asp Phe Ala Gly Gly Leu Met Cys
                    150
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Ala Leu Gly Ile Ile Met Ala Leu Phe Asp Arg Thr Arg Thr Asp Lys
                165
                                    170
Gly Gln Val Ile Asp Ala Asn Met Val Glu Gly Thr Ala Tyr Leu Ser
                                185
Ser Phe Leu Trp Lys Thr Gln Lys Ser Ser Leu Trp Glu Ala Pro Arg
                            200
Gly Gln Asn Met Leu Asp Gly Gly Ala Pro Phe Tyr Thr Tyr Arg
                        215
                                            220
Thr Ala Asp Gly Glu Phe Met Ala Val Gly Ala Ile Glu Pro Gln Phe
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                                        235
Tyr Glu Leu Leu Ile Lys Gly Leu Gly Leu Lys Ser Asp Glu Leu Pro
                245
                                    250
Asn Gln Met Ser Met Asp Asp Trp Pro Glu Met Lys Lys Lys Phe Ala
                                265
Asp Val Phe Ala Lys Lys Thr Lys Ala Glu Trp Cys Gln Ile Phe Asp
                            280
                                                285
Gly Thr Asp Ala Cys Val Thr Pro Val Leu Thr Phe Glu Glu Val Val
                        295
                                            300
His His Asp His Asn Lys Glu Arg Gly Ser Phe Ile Thr Ser Glu Glu
                    310
                                        315
Gln Asp Val Ser Pro Arg Pro Ala Pro Leu Leu Leu Asn Thr Pro Ala
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                                    330
Ile Pro Ser Phe Lys Arg Asp Pro Phe Ile Gly Glu His Thr Glu Glu
            340
                                345
                                                    350
Ile Leu Glu Glu Phe Gly Phe Ser Arg Glu Glu Ile Tyr Gln Leu Asn
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Ser Asp Lys Ile Ile Glu Ser Asn Lys Val Lys Ala Ser Leu
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<400> 109

<213> Homo sapien

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900
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gagegtetga agegeaegte eeagaaggtg gaettggeae tgaaacaget gggacacate
                                                                      1020
                                                                      1080
cgcgagtacg aacagcgcct gaaagtgctg gagcgggagg tccagcagtg tagccgcgtc
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                                                                      1320
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                                                                      1440
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      <210> 110
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1260

1289

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<213> Homo sapien

<400> 113

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355
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Thr Cys Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu
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Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr Leu Ala
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                                        395
Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro Lys Tyr Arg Gly
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Asp Thr Gly Gly Ala Ser Ser Glu Asp Ser Leu Met Thr Ser Phe Leu
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Pro Gly Pro Lys Pro Gly Ala Pro Phe Pro Asn Gly His Val Gly Ala
                           440
Gly Gly Ser Gly Leu Leu Pro Pro Pro Pro Ala Leu Cys Gly Ala Ser
                        455
Ala Cys Asp Val Ser Val Arg Val Val Gly Glu Pro Thr Glu Ala
                                        475
Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile Leu Asp
                                    490
Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met Gly Ser
           500
                                505
Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met Val Ser Ala Ala
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<211> 241

<212> PRT

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145
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                                       155
                                                          160
Ser Pro Tyr Phe Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn
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                                   170
                                                      175
Asp Asn Val Thr Asn Thr Ala Asn Glu Thr Cys Thr Lys Gln Lys Ala
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                               185
His Asp Gln Lys Val Glu Gly Cys Phe Asn Gln Leu Leu Tyr Asp Ile
                           200
Arg Thr Asn Ala Val Thr Val Gly Gly Val Ala Ala Gly Ile Gly Gly
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Leu Glu Leu Ala Ala Met Ile Val Ser Met Tyr Leu Tyr Cys Asn Leu
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ttagtc
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     <211> 282
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                                                                    120
agactttact attttcatat tttaagacac atgatttatc ctattttagt aacctggttc
                                                                    180
atacgttaaa caaaggataa tgtgaacagc agagaggatt tgttggcaga aaatctatgt
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tcaatcinga actatciana tcacagacat tictaticci ti
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     <211> 305
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<213> Homo sapien

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                                                                         120
aataaggcaa aatatatgaa acaacaggtc tcgagatatt ggaaatcagt caatgaagga
                                                                         180
tactgatccc tgatcactgt cctaatgcag gatgtgggaa acagatgagg tcacctctgt
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gactgcccca gcttactgcc tgtagagagt ttctangctg cagttcagac agggagaaat
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tgggt
                                                                         305
      <210> 118
      <211> 71
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
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      <400> 118
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aantcctggg t
                                                                          71
      <210> 119
      <211> 212
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      <400> 119
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                                                                         120
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      <211> 90
      <212> DNA
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      <221> misc_feature
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      <223> n = A, T, C or G
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<210> 121 <211> 218 <212> DNA <213> Homo sapien	
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ctacagtctg catttggcag aaatgaagat gaatttggat			180
ttgcctcacc aaacaaaagt gaaacaactg agagaaaatt			240
ctcttgaagt atcagtcact tttgagaatg tttcttagtt			300
catggtgggg gtcttgcatc tgtaagaatg gaattgattt caggaaacat cagaaccact attttctagc cctctgtcag			360 420
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ageaagaacg acaccecce coagggacca coaaacacce	acaaaaaccc	90	112
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		5 0	
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ttctctctga agtctaggtt acccattttg gggacccatt			180
ccaaagcatt tggacagttt cttgttgtgt tttagaatgg			240
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<211> 192			

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<212> DNA
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      <220>
      <221> misc_feature
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tagcacattc atctgtgata naaagatagg tgagtttcat ttccttcacg ttggccaatg
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qataaacaaa qt
                                                                        192
      <210> 130
      <211> 362
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
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      <223> n = A, T, C or G
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gg
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      <211> 332
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      <223> n = A, T, C or G
      <400> 132
actittgcca tittgtatat ataaacaatc tigggacatt ciccigaaaa ciaggigtcc
                                                                          60
agtggctaag agaactcgat ttcaagcaat tctgaaagga aaaccagcat gacacagaat
                                                                         120
ctcaaattcc caaacagggg ctctgtggga aaaatgaggg aggacctttg tatctcgggt
                                                                         180
tttagcaagt taaaatgaan atgacaggaa aggcttattt atcaacaaag agaagagttg
                                                                         240
ggatgcttct aaaaaaaact ttggtagaga aaataggaat gctnaatcct agggaagcct
                                                                         300
gtaacaatct acaattggtc ca
                                                                         322
      <210> 133
      <211> 278
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(278)
      \langle 223 \rangle n = A,T,C or G
      <400> 133
acaagcette acaagtttaa etaaattggg attaatettt etgtanttat etgeataatt
                                                                         60
cttgtttttc tttccatctg gctcctgggt tgacaatttg tggaaacaac tctattgcta
                                                                         120
ctatttaaaa aaaatcacaa atctttccct ttaagctatg ttnaattcaa actattcctg
                                                                        180
ctattcctgt tttgtcaaag aaattatatt tttcaaaata tgtntatttg tttgatgggt
                                                                         240
cccacgaaac actaataaaa accacagaga ccagcctg
                                                                        278
      <210> 134
      <211> 121
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(121)
      <223> n = A, T, C or G
      <400> 134
gtttanaaaa cttgtttagc tccatagagg aaagaatgtt aaactttgta ttttaaaaca
                                                                         60
tgattctctg aggttaaact tggttttcaa atgttatttt tacttgtatt ttgcttttgg
                                                                        120
                                                                        121
```

```
<211> 350
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(350)
      \langle 223 \rangle n = A,T,C or G
      <400> 135
acttanaacc atgcctagca catcagaatc cctcaaagaa catcagtata atcctatacc
                                                                         60
atancaagtg gtgactggtt aagcgtgcga caaaggtcag ctggcacatt acttgtgtgc
                                                                         120
aaacttgata cttttgttct aagtaggaac tagtatacag tncctaggan tggtactcca
                                                                         180
gggtgccccc caactectgc ageegeteet etgtgccagn eeetgnaagg aacttteget
                                                                         240
ccaectcaat caagecetgg gecatgetac etgeaattgg etgaacaaac gtttgetgag
                                                                         300
ttcccaagga tgcaaagcct ggtgctcaac tcctggggcg tcaactcagt
                                                                         350
      <210> 136
      <211> 399
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(399)
      <223> n = A, T, C or G
      <400> 136
tgtaccgtga agacgacaga agttgcatgg cagggacagg gcagggccga ggccagggtt
                                                                         60
gctgtgattg tatccgaata ntcctcgtga gaaaagataa tgagatgacg tgagcagcct
                                                                         120
gcagacttgt gtctgccttc aanaagccag acaggaaggc cctgcctgcc ttggctctga
                                                                         180
cctggcggcc agccagccag ccacaggtgg gcttcttcct tttgtggtga caacnccaag
                                                                         240
aaaactgcag aggcccaggg tcaggtgtna gtgggtangt gaccataaaa caccaggtgc
                                                                         300
teccaggaac cegggeaaag gecateeeca cetacageea geatgeecae tggegtgatg
                                                                         360
ggtgcagang gatgaagcag ccagntgttc tgctgtggt
                                                                         399
      <210> 137
      <211> 165
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(165)
      <223> n = A, T, C \text{ or } G
      <400> 137
actggtgtgg tngggggtga tgctggtggt anaagttgan gtgacttcan gatggtgtgt
                                                                         60
ggaggaagtg tgtgaacgta gggatgtaga ngttttggcc gtgctaaatg agcttcggga
                                                                        120
ttggctggtc ccactggtgg tcactgtcat tggtggggtt cctgt
                                                                         165
```

<212> DNA

```
<210> 138
      <211> 338
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(338)
      <223> n = A, T, C \text{ or } G
      <400> 138
actcactgga atgccacatt cacaacagaa tcagaggtct gtgaaaacat taatggctcc
                                                                         60
ttaacttctc cagtaagaat cagggacttg aaatggaaac gttaacagcc acatgcccaa
                                                                        120
tgctgggcag tctcccatgc cttccacagt gaaagggctt gagaaaaatc acatccaatg
                                                                        180
tcatgtgttt ccagccacac caaaaggtgc ttggggtgga gggctggggg catananggt
                                                                        240
cangeeteag gaageeteaa gtteeattea getttgeeae tgtaeattee eeatntttaa
                                                                        300
aaaaactgat gccttttttt tttttttttg taaaattc
                                                                        338
      <210> 139
      <211> 382
      <212> DNA
      <213> Homo sapien
      <400> 139
gggaatettg gtttttggca tetggtttge etatageega ggeeaetttg acagaacaaa
                                                                         60
gaaagggact tcgagtaaga aggtgattta cagccagcct agtgcccgaa gtgaaggaga
                                                                        120
atteaaacag acctegteat teetggtgtg ageetggteg geteacegee tateatetge
                                                                        180
atttgcctta ctcaggtgct accggactct ggcccctgat gtctgtagtt tcacaggatg
                                                                        240
cettatttgt ettetacace ceacagggee ceetacttet teggatgtgt ttttaataat
                                                                        300
gteagetatg tgececatee teetteatge esteecteec ttteetacea etgetgagtg
                                                                        360
gcctggaact tgtttaaagt gt
                                                                        382
      <210> 140
      <211> 200
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(200)
      \langle 223 \rangle n = A,T,C or G
      <400> 140
accaaanctt ctttctgttg tgttngattt tactataggg gtttngcttn ttctaaanat
                                                                         60
acttttcatt taacancttt tgttaagtgt caggetgcac tttgctccat anaattattg
                                                                        120
ttttcacatt tcaacttgta tgtgtttgtc tcttanagca ttggtgaaat cacatatttt
                                                                        180
atattcagca taaaggagaa
                                                                        200
      <210> 141
      <211> 335
```

```
<213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(335)
      <223> n = A, T, C or G
      <400> 141
actttatttt caaaacactc atatgttgca aaaaacacat agaaaaataa agtttggtgg
                                                                        60
gggtgctgac taaacttcaa gtcacagact tttatgtgac agattggagc agggtttgtt
                                                                        120
atgcatgtag agaacccaaa ctaatttatt aaacaggata gaaacaggct gtctqqgtqa
                                                                        180
aatggttctg agaaccatcc aattcacctg tcagatgctg atanactagc tcttcagatg
                                                                        240
tttttctacc agttcagaga tnggttaatg actanttcca atggggaaaa agcaaqatqq
                                                                        300
attcacaaac caagtaattt taaacaaaga cactt
                                                                        335
      <210> 142
      <211> 459
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(459)
      <223> n = A, T, C or G
      <400> 142
accaggttaa tattgccaca tatatccttt ccaattgcgg gctaaacaga cgtgtattta
                                                                        60
gggttgttta aagacaaccc agcttaatat caagagaaat tgtgaccttt catggagtat
                                                                       120
ctgatggaga aaacactgag ttttgacaaa tcttatttta ttcagatagc aqtctgatca
                                                                       180
cacatggtcc aacaacactc aaataataaa tcaaatatna tcagatgtta aagattggtc
                                                                       240
ttcaaacatc atagccaatg atgccccgct tgcctataat ctctccgaca taaaaccaca
                                                                       300
tcaacacctc agtggccacc aaaccattca gcacagcttc cttaactgtg agctgtttga
                                                                       360
agctaccagt ctgagcacta ttgactatnt ttttcangct ctgaatagct ctagggatct
                                                                       420
cagcangggt gggaggaacc agctcaacct tggcgtant
                                                                       459
      <210> 143
      <211> 140
      <212> DNA
      <213> Homo sapien
      <400> 143
acatttcctt ccaccaagtc aggactcctg gcttctgtgg gagttcttat cacctgaggg
                                                                        60
aaatccaaac agtctctcct agaaaggaat agtgtcacca accccaccca tctccctqaq
                                                                       120
accatccgac ttccctgtgt
                                                                       140
      <210> 144
      <211> 164
      <212> DNA
      <213> Homo sapien
      <220>
```

```
<221> misc feature
      <222> (1)...(164)
      <223> n = A, T, C \text{ or } G
      <400> 144
acttcagtaa caacatacaa taacaacatt aagtgtatat tgccatcttt gtcattttct
                                                                          60
atctatacca ctctcccttc tgaaaacaan aatcactanc caatcactta tacaaatttg
                                                                         120
aggcaattaa tccatatttg ttttcaataa ggaaaaaaag atgt
                                                                         164
      <210> 145
      <211> 303
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(303)
      \langle 223 \rangle n = A,T,C or G
      <400> 145
acgtagacca tccaactttg tatttgtaat ggcaaacatc cagnagcaat tcctaaacaa
                                                                         60
actggagggt atttataccc aattatccca ttcattaaca tgccctcctc ctcaggctat
                                                                         120
gcaggacage tatcataagt eggeccagge atecagatae taccatttgt ataaacttca
                                                                         180
gtaggggagt ccatccaagt gacaggtcta atcaaaggag gaaatggaac ataagcccag
                                                                         240
tagtaaaatn ttgcttagct gaaacagcca caaaagactt accgccgtgg tgattaccat
                                                                         300
                                                                         303
      <210> 146
      <211> 327
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(327)
      <223> n = A, T, C or G
      <400> 146
actgcagctc aattagaagt ggtctctgac tttcatcanc ttctccctgg gctccatgac
                                                                         60
actggcctgg agtgactcat tgctctggtt ggttgagaga gctcctttqc caacaqqcct
                                                                         120
ccaagtcagg gctgggattt gtttcctttc cacattctag caacaatatg ctggccactt
                                                                         180
cctgaacagg gagggtggga ggagccagca tggaacaagc tgccactttc taaagtagcc
                                                                         240
agacttgccc ctgggcctgt cacacctact gatgaccttc tgtgcctgca ggatggaatg
                                                                         300
taggggtgag ctgtgtgact ctatggt
                                                                         327
      <210> 147
      <211> 173
      <212> DNA
      <213> Homo sapien
      <220>
```

```
<221> misc feature
      <222> (1)...(173)
      <223> n = A, T, C \text{ or } G
      <400> 147
acattgtttt tttgagataa agcattgana gagctctcct taacgtgaca caatggaagg
                                                                         60
actggaacac atacccacat ctttgttctg agggataatt ttctgataaa gtcttgctgt
                                                                        120
atattcaagc acatatgtta tatattattc agttccatgt ttatagccta gtt
                                                                        173
      <210> 148
      <211> 477
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(477)
      <223> n = A, T, C \text{ or } G
      <400> 148
acaaccactt tatctcatcg aatttttaac ccaaactcac tcactgtgcc tttctatcct
                                                                         60
atgggatata ttatttgatg ctccatttca tcacacatat atgaataata cactcatact
                                                                        120
gccctactac ctgctgcaat aatcacattc ccttcctgtc ctgaccctga agccattggg
                                                                        180
gtggtcctag tggccatcag tccangcctg cacettgage cettgagete cattgeteac
                                                                        240
nccancecae etcacegace ceatectett acacagetae etcettgete tetaacecea
                                                                        300
tagattatnt ccaaattcag tcaattaagt tactattaac actctacccg acatgtccag
                                                                        360
caccactggt aagcettete cagecaacae acacacaca acacneacae acacacatat
                                                                        420
ccaggcacag gctacctcat cttcacaatc acccctttaa ttaccatgct atggtgg
                                                                        477
      <210> 149
      <211> 207
      <212> DNA
      <213> Homo sapien
      <400> 149
acagttgtat tataatatca agaaataaac ttgcaatgag agcatttaag agggaagaac
                                                                         60
taacgtattt tagagagcca aggaaggttt ctgtggggag tgggatgtaa ggtggggcct
                                                                        120
gatgataaat aagagtcagc caggtaagtg ggtggtgtgg tatgggcaca gtgaagaaca
                                                                        180
tttcaggcag agggaacagc agtgaaa
                                                                        207
      <210> 150
      <211> 111
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(111)
      <223> n = A, T, C or G
      <400> 150
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accttgattt cattgctgct ctgatggaaa cccaactatc taatttagct aaaaccacttaaatg tggtcagtgt ttggacttgt taactantgg catctttggg t	catggg 60 111
<210> 151 <211> 196 <212> DNA <213> Homo sapien	
<400> 151	
agegeggeag gteatattga acatteeaga tacetateat tactegatge tgttg ageaagatgg etttgaacte agggteacea ceagetattg gaeettaeta tgaaa	
ggataccaac cggaaaaccc ctatcccgca cagcccactg tggtccccac tgtct	
gtgcatccgg ctcagt	196
<210> 152	
<211> 132	
<212> DNA	
<213> Homo sapien	
<400> 152	
acagcacttt cacatgtaag aagggagaaa ttcctaaatg taggagaaag ataac cttccccttt tcatctagtg gtggaaacct gatgctttat gttgacagga ataga	-
gagggagttt gt	132
<210> 153	
<211> 285	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)(285) <223> n = A,T,C or G	
(223) 11 - 11/1/6 01 0	
<400> 153	
acaanaccca nganaggcca ctggccgtgg tgtcatggcc tccaaacatg aaagt cttctgctct tatgtcctca tctgacaact ctttaccatt tttatcctcg ctcag	
gcacatcaat aaagtccaaa gtcttggact tggccttggc ttggaggaag tcatc	
cctggctagt gagggtgcgg cgccgctcct ggatgacggc atctgtgaag tcgtg	
gtctgcaggc cctgtggaag cgccgtccac acggagtnag gaatt	285
<210> 154	
<211> 333	
<212> DNA <213> Homo sapien	
<400> 154	
accacagtee tgttgggeea gggetteatg accetttetg tgaaaageea tatta	itcacc 60
accccaaatt tttccttaaa tatctttaac tgaaggggtc agcctcttga ctgca	
cctaagccgg ttacacagct aactcccact ggccctgatt tgtgaaattg ctgct	
attggcacag gagtcgaagg tgttcagctc ccctcctccg tggaacgaga ctctg	gatttg 240

```
agtttcacaa attctcgggc cacctcgtca ttgctcctct gaaataaaat ccggagaatg
                                                                        300
gtcaggcctg tctcatccat atggatcttc cgg
                                                                        333
      <210> 155
      <211> 308
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(308)
      \langle 223 \rangle n = A,T,C or G
      <400> 155
actggaaata ataaaaccca catcacagtg ttgtgtcaaa gatcatcagg gcatggatgg
                                                                         60
gaaagtgctt tgggaactgt aaagtgccta acacatgatc gatgattttt gttataatat
                                                                        120
ttgaatcacg gtgcatacaa actctcctgc ctgctcctcc tgggccccag ccccagcccc
                                                                        180
atcacagete actgetetgt teatecagge ceageatgta gtggetgatt ettettgget
                                                                        240
gcttttagcc tccanaagtt tctctgaagc caaccaaacc tctangtgta aggcatgctg
                                                                        300
gccctggt
                                                                        308
      <210> 156
      <211> 295
      <212> DNA
      <213> Homo sapien
      <400> 156
accttgctcg gtgcttggaa catattagga actcaaaata tgagatgata acagtgccta
                                                                         60
ttattgatta ctgagagaac tgttagacat ttagttgaag attttctaca caggaactga
                                                                        120
gaataggaga ttatgtttgg ccctcatatt ctctcctatc ctccttgcct cattctatgt
                                                                        180
ctaatatatt ctcaatcaaa taaggttagc ataatcagga aatcgaccaa ataccaatat
                                                                        240
aaaaccagat gtctatcctt aagattttca aatagaaaac aaattaacag actat
                                                                        295
      <210> 157
      <211> 126
      <212> DNA
      <213> Homo sapien
      <400> 157
acaagtttaa atagtgctgt cactgtgcat gtgctgaaat gtgaaatcca ccacatttct
                                                                         60
gaagagcaaa acaaattetg teatgtaate tetatettgg gtegtgggta tatetgteee
                                                                        120
cttagt
                                                                        126
      <210> 158
      <211> 442
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(442)
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## <223> n = A, T, C or G<400> 158 acccactggt cttggaaaca cccatcctta atacgatgat ttttctgtcg tgtgaaaatg 60 aanccagcag gctgccccta gtcagtcctt ccttccagag aaaaagagat ttgagaaagt 120 gcctgggtaa ttcaccatta atttcctccc ccaaactetc tgagtettcc cttaatattt 180 ctggtggttc tgaccaaagc aggtcatggt ttgttgagca tttggggatcc cagtgaagta 240 natgtttgta gccttgcata cttagccctt cccacgcaca aacggagtgg cagagtggtg 300 ccaaccctgt tttcccagtc cacgtagaca gattcacagt gcggaattct ggaagctgga 360 nacagacggg ctctttgcag agccgggact ctgagangga catgagggcc tctgcctctg 420 tqttcattct ctgatqtcct qt 442 <210> 159 <211> 498 <212> DNA <213> Homo sapien <220> <221> misc\_feature <222> (1)...(498) $\langle 223 \rangle$ n = A,T,C or G <400> 159 60 acttccaggt aacgttgttg tttccgttga gcctgaactg atgggtgacg ttgtaggttc tccaacaaga actgaggttg cagagcgggt agggaagagt gctgttccag ttgcacctgg 120 180 gctgctgtgg actgttgttg attcctcact acggcccaag gttgtggaac tggcanaaag gtgtgttgtt gganttgage tegggegget gtggtaggtt gtgggetett caacagggge 240 tgctgtggtg ccgggangtg aangtgttgt gtcacttgag cttggccagc tctggaaagt 300 antanattct tcctgaaggc cagcgcttgt ggagctggca ngggtcantg ttgtgtgtaa 360 420 cqaaccaqtq ctqctqtqqq tqqqtqtana tcctccacaa aqcctqaagt tatqqtqtcn tcaggtaana atgtggtttc agtgtccctg ggcngctgtg gaaggttgta nattgtcacc 480 aagggaataa gctgtggt 498 <210> 160 <211> 380 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1)...(380) <223> n = A,T,C or G<400> 160 acctgcatcc agetteectg ccaaacteac aaggagacat caacctetag acagggaaac 60 agetteagga taetteeagg agacagagee accageagea aaacaaatat teecatgeet 120 ggagcatggc atagaggaag ctganaaatg tggggtctga ggaagccatt tgagtctggc 180 cactagacat ctcatcagcc acttgtgtga agagatgccc catgacccca gatgcctctc 240 ccaccettae etecatetea cacaettgag etttecaete tgtataatte taacateetg 300

gagaaaaatg gcagtttgac cgaacctgtt cacaacggta gaggctgatt tctaacgaaa

cttgtagaat gaagcctgga

360

```
<210> 161
      <211> 114
      <212> DNA
      <213> Homo sapien
      <400> 161
actocacate cectetgage aggeggttgt egtteaaggt gtatttggee ttgeetgtea
                                                                         60
cactgtccac tggcccctta tccacttggt gcttaatccc tcgaaagagc atgt
                                                                        114
      <210> 162
      <211> 177
      <212> DNA
      <213> Homo sapien
      <400> 162
actttctgaa tcgaatcaaa tgatacttag tgtagtttta atatcctcat atatatcaaa
                                                                         60
gttttactac tctgataatt ttgtaaacca ggtaaccaga acatccagtc atacagcttt
                                                                         120
tggtgatata taacttggca ataacccagt ctggtgatac ataaaactac tcactgt
                                                                         177
      <210> 163
      <211> 137
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(137)
      <223> n = A, T, C \text{ or } G
      <400> 163
catttataca gacaggcgtg aagacattca cgacaaaaac gcgaaattct atcccgtgac
                                                                         60
canagaaggc agctacggct actcctacat cctggcgtgg gtggccttcg cctgcacctt
                                                                        120
                                                                        137
catcagcggc atgatgt
      <210> 164
      <211> 469
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(469)
      <223> n = A, T, C \text{ or } G
      <400> 164
cttatcacaa tgaatgttct cctqqqcaqc qttqtqatct ttqccacctt cqtqacttta
                                                                         60
tgcaatgcat catgctattt catacctaat gagggagttc caggagattc aaccaggaaa
                                                                        120
tgcatggatc tcaaaggaaa caaacaccca ataaactcgg agtggcagac tgacaactgt
                                                                        180
gagacatgca cttgctacga aacagaaatt tcatgttgca cccttgtttc tacacctgtg
                                                                        240
ggttatgaca aagacaactg ccaaagaatc ttcaagaagg aggactgcaa gtatatcgtg
                                                                        300
```

```
gtggagaaga aggacccaaa aaagacctgt tctgtcagtg aatggataat ctaatgtgct
                                                                         360
totagtaggc acagggetee caggecagge ctcattetee tetggeetet aatagteaat
                                                                         420
gattgtgtag ccatgcctat cagtaaaaag atntttgagc aaacacttt
                                                                         469
      <210> 165
      <211> 195
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(195)
      <223> n = A, T, C \text{ or } G
      <400> 165
                                                                          60
acagtttttt atanatatcg acattgccgg cacttgtgtt cagtttcata aagctggtgg
atcogotyte atcoactatt cottygotag agtaaaaatt attottatag cocatytoco
                                                                         120
tgcaggccgc ccgcccgtag ttctcgttcc agtcgtcttg gcacacaggg tgccaggact
                                                                         180
                                                                         195
tcctctgaga tgagt
      <210> 166
      <211> 383
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(383)
      <223> n = A, T, C or G
      <400> 166
                                                                          60
acatettagt agtgtggeac atcaggggge catcagggte acagteacte atagcetege
cgaggtcgga gtccacacca ccggtgtagg tgtgctcaat cttgggcttg gcgcccacct
                                                                         120
ttggagaagg gatatgctgc acacacatgt ccacaaagcc tgtgaactcg ccaaagaatt
                                                                         180
tttgcagacc agcctgagca aggggcggat gttcagcttc agctcctcct tcgtcaggtg
                                                                         240
gatgecaace tegtetangg teegtgggaa getggtgtee aenteaceta caacetggge
                                                                         300
gangatetta taaagagget eenagataaa etecaegaaa ettetetggg agetgetagt
                                                                         360
nggggccttt ttggtgaact ttc
                                                                         383
      <210> 167
      <211> 247
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(247)
      \langle 223 \rangle n = A,T,C or G
      <400> 167
acagagecag acettggeca taaatgaane agagattaag actaaacece aagteganat
                                                                          60
```

```
tggagcagaa actggagcaa gaagtgggcc tggggctgaa gtagagacca aggccactgc
                                                                         120
tatanccata cacaqaqcca acteteaqqe caaqqenatq qttqqqqcaq anccaqaqae
                                                                         180
tcaatctgan tccaaagtgg tggctggaac actggtcatg acanaggcag tgactctgac
                                                                         240
tgangtc
                                                                         247
      <210> 168
      <211> 273
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(273)
      <223> n = A, T, C \text{ or } G
      <400> 168
acttctaagt tttctagaag tggaaggatt gtantcatcc tgaaaatggg tttacttcaa
                                                                          60
aatccctcan ccttgttctt cacnactgtc tatactgana gtgtcatgtt tccacaaagg
                                                                         120
gctgacacct gagcctgnat tttcactcat ccctgagaag ccctttccag tagggtgggc
                                                                         180
aattoccaac ttocttgcca caagettecc aggetttete ceetggaaaa etecagettg
                                                                         240
agtcccagat acactcatgg gctgccctgg gca
                                                                         273
      <210> 169
      <211> 431
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(431)
      <223> n = A, T, C \text{ or } G
      <400> 169
acageettgg etteeceaaa etecacagte teagtgeaga aagateatet tecageagte
                                                                          60
agctcagacc agggtcaaag gatgtgacat caacagtttc tggtttcaga acaggttcta
                                                                         120
ctactgtcaa atgacccccc atacttcctc aaaggctgtg gtaagttttg cacaggtgag
                                                                         180
ggcagcagaa agggggtant tactgatgga caccatcttc tctgtatact ccacactgac
                                                                         240
cttgccatgg gcaaaggccc ctaccacaaa aacaatagga tcactgctgg gcaccagetc
                                                                         300
acgcacatca ctgacaaccg ggatggaaaa agaantgcca actttcatac atccaactgg
                                                                         360
aaagtgatet gataetggat tettaattae etteaaaage ttetggggge eateagetge
                                                                         420
tcgaacactg a
                                                                         431
      <210> 170
      <211> 266
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(266)
      \langle 223 \rangle n = A,T,C or G
```

```
<400> 170
acctgtgggc tgggctgtta tgcctgtgcc ggctgctgaa agggagttca gaggtggagc
                                                                      60
tcaaggaget etgeaggeat tttgecaane etetecanag canagggage aacetacaet
                                                                     120
ccccgctaga aagacaccag attggagtcc tgggaggggg agttggggtg ggcatttgat
                                                                     180
gtatacttgt cacctgaatg aangagccag agaggaanga gacgaanatg anattggcct
                                                                     240
tcaaagctag gggtctggca ggtgga
                                                                     266
      <210> 171
      <211> 1248
      <212> DNA
      <213> Homo sapien
     <220>
      <221> misc_feature
      <222> (1)...(1248)
     <223> n = A, T, C or G
      <400> 171
                                                                      60
ggcagccaaa tcataaacgg cgaggactgc agcccgcact cgcagccctg gcaggcggca
ctggtcatgg aaaacgaatt gttctgctcg ggcgtcctgg tgcatccgca gtgggtgctg
                                                                     120
                                                                     180
teageegeae aetgttteea gaagtgagtg cagageteet acaccategg getgggeetg
cacagtettg aggeegacea agageeaggg ageeagatgg tggaggeeag ceteteegta
                                                                     240
                                                                     300
eggeacecag agtacaacag accettgete getaacgace teatgeteat caagttggae
gaateegtgt eegagtetga caecateegg ageateagea ttgettegea gtgeeetaee
                                                                     360
                                                                     420
gcggggaact cttgcctcgt ttctggctgg ggtctgctgg cgaacggcag aatgcctacc
gtgctgcagt gcgtgaacgt gtcggtggtg tctgaggagg tctgcagtaa gctctatgac
                                                                     480
                                                                     540
ccgctgtacc accccagcat gttctgcgcc ggcggagggc aagaccagaa ggactcctgc
aacggtgact ctggggggcc cctgatctgc aacgggtact tgcagggcct tgtgtctttc
                                                                     600
ggaaaagccc cgtgtggcca agttggcgtg ccaggtgtct acaccaacct ctgcaaattc
                                                                     660
                                                                     720
actgagtgga tagagaaaac cgtccaggcc agttaactct ggggactggg aacccatgaa
attgaccccc aaatacatcc tgcggaagga attcaggaat atctgttccc agcccctcct
                                                                     780
ccctcaggcc caggagtcca ggcccccagc ccctcctccc tcaaaccaag ggtacagatc
                                                                     840
eccagecet ceteceteag acceaggagt ceagacece cageceetee teceteagae
                                                                     900
ccaggagtcc agecettect cecteagace caggagteca gacececag eccetectee
                                                                     960
ctcaqaccca qqqgtccaqq cccccaaccc ctcctccctc aqactcaqaq qtccaagccc
                                                                    1020
ccaaccente attecceaga eccagaggte caggteccag eccetentee etcagaceca
                                                                    1080
geggteeaat geeacetaga etnteeetgt acaeagtgee eeettgtgge aegttgaeee
                                                                    1140
aaccttacca gttggttttt catttttngt ccctttcccc tagatccaga aataaagttt
                                                                    1200
1248
      <210> 172
      <211> 159
      <212> PRT
      <213> Homo sapien
      <220>
      <221> VARIANT
      <222> (1)...(159)
     <223> Xaa = Any Amino Acid
```

```
<400> 172
Met Val Glu Ala Ser Leu Ser Val Arq His Pro Glu Tyr Asn Arq Pro
                 5
                                    10
Leu Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser
            20
                                25
Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr
Ala Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly
                        55
Arg Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu
                                        75
Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe
Cys Ala Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser
            100
                                105
                                                    110
Gly Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe
                            120
Gly Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn
                        135
                                            140
Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
145
                    150
                                        155
      <210> 173
      <211> 1265
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(1265)
      <223> n = A, T, C or G
      <400> 173
ggcagcccgc actcgcagcc ctggcaggcg gcactggtca tggaaaacga attgttctgc
                                                                        60
tegggegtee tggtgeatee geagtgggtg etgteageeg cacactgttt ecagaactee
                                                                       120
tacaccateg ggetgggeet geacagtett gaggeegaee aagageeagg gageeagatg
                                                                       180
gtggaggcca gecteteegt aeggeaeeca gagtacaaca gaeeettget egetaaegae
                                                                       240
ctcatgetca teaagttgga egaateegtg teegagtetg acaecateeg gageateage
                                                                       300
attgcttcgc agtgccctac cgcggggaac tcttgcctcg tttctggctg gggtctgctg
                                                                       360
gcgaacggtg agctcacggg tgtgtgtctg ccctcttcaa ggaggtcctc tgcccagtcg
                                                                       420
cgggggetga cccagagetc tgcgtcccag gcagaatgcc taccgtgctg cagtgcgtga
                                                                       480
acgtgtcggt ggtgtctgag gaggtctgca gtaagctcta tgacccgctg taccacccca
                                                                       540
gcatgttctg cgccggcgga gggcaagacc agaaggactc ctgcaacggt gactctgggg
                                                                       600
ggcccctgat ctgcaacggg tacttgcagg gccttgtgtc tttcggaaaa gccccgtgtg
                                                                       660
                                                                       720
gccaagttgg cgtgccaggt gtctacacca acctctgcaa attcactgag tggatagaga
aaaccgtcca ggccagttaa ctctggggac tgggaaccca tgaaattgac ccccaaatac
                                                                       780
atcctgcgga aggaattcag gaatatctqt tcccagcccc tcctccctca gqcccaggag
                                                                       840
tocaggecce cagecectee teecteaaac caagggtaca gateeccage cecteetee
                                                                       900
tcagacccag gagtccagac ccccagccc ctcctccctc agacccagga gtccagccc
                                                                       960
tecteentea gaccaggag tecagacece ecagececte etceeteaga eccaggggtt
                                                                      1020
gaggeeecca accecteete etteagagte agaggteeaa geeeccaace eetegtteee
```

```
cagacccaga ggtnnaggtc ccagcccctc ttccntcaga cccagnggtc caatgccacc
                                                                       1140
tagattttcc ctgnacacag tgcccccttg tggnangttg acccaacctt accagttggt
                                                                       1200
ttttcatttt tngtcccttt cccctagatc cagaaataaa gtttaagaga ngngcaaaaa
                                                                       1260
aaaaa
                                                                       1265
      <210> 174
      <211> 1459
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(1459)
      <223> n = A, T, C or G
      <400> 174
ggtcagccgc acactgtttc cagaagtgag tgcagagctc ctacaccatc gggctgggcc
                                                                        60
tgcacagtct tgaggccgac caagagccag ggagccagat ggtggaggcc agcctctccg
                                                                        120
tacggcaccc agagtacaac agacccttgc tegetaacga ceteatgete atcaagttgg
                                                                        180
acgaatccgt gtccgagtct gacaccatcc ggagcatcag cattgcttcg caqtgcccta
                                                                        240
ccgcggggaa ctcttgcctc gtttctggct ggggtctgct ggcgaacggt gagctcacgg
                                                                        300
gtgtgtgtet geeetettea aggaggteet etgeeeagte gegggggetg acceagaget
                                                                        360
ctgcgtccca ggcagaatgc ctaccgtgct gcagtgcgtg aacgtgtcgg tggtgtctga
                                                                        420
ngaggtetge antaagetet atgacceget gtaccacece ancatgttet gegeeggegg
                                                                        480
agggcaagac cagaaggact cctgcaacgt gagagagggg aaaggggagg gcaggcgact
                                                                        540
cagggaaggg tggagaaggg ggagacagag acacacaggg ccgcatggcg agatgcagag
                                                                        600
atggagagac acacagggag acagtgacaa ctagagagag aaactgagag aaacagagaa
                                                                        660
ataaacacag gaataaagag aagcaaagga agagagaaac agaaacagac atggggaggc
                                                                        720
agaaacacac acacatagaa atgcagttga ccttccaaca gcatggggcc tgagggcggt
                                                                        780
gacctccacc caatagaaaa teetettata aettttgaet eeccaaaaac etgactagaa
                                                                        840
atagectaet gttgaegggg ageettaeea ataacataaa tagtegattt atgeataegt
                                                                       900
tttatgcatt catgatatac ctttgttgga attttttgat atttctaagc tacacagttc
                                                                       960
gtctgtgaat ttttttaaat tgttgcaact ctcctaaaat ttttctgatg tgtttattga
                                                                       1020
aaaaatccaa gtataagtgg acttgtgcat tcaaaccagg gttgttcaag ggtcaactgt
                                                                       1080
gtacccagag ggaaacagtg acacagattc atagaggtga aacacgaaga gaaacaggaa
                                                                      1140
aaatcaagac tetacaaaga ggetgggeag ggtggeteat geetgtaate eeageaettt
                                                                       1200
gggaggcgag gcaggcagat cacttgaggt aaggagttca agaccagcct ggccaaaatg
                                                                      1260
gtgaaatcct gtctgtacta aaaatacaaa agttagctgg atatggtggc aggcgcctgt
                                                                      1320
aatcccagct acttgggagg ctgaggcagg agaattgctt gaatatggga ggcagaggtt
                                                                      1380
gaagtgagtt gagatcacac cactatactc cagetggggc aacagagtaa gactetgtet
                                                                      1440
caaaaaaaa aaaaaaaaa
                                                                      1459
      <210> 175
      <211> 1167
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(1167)
      <223> n = A, T, C \text{ or } G
```

60

120

180

240

300

360

420 480

540 600

660 720

780 840

900 960

```
<400> 175
gegeageeet ggeaggegge aetggteatg gaaaaegaat tgttetgete gggegteetg
gtgcatccgc agtgggtgct gtcagccgca cactgtttcc agaactccta caccatcggg
ctgggcctgc acagtcttga ggccgaccaa gagccaggga gccagatggt ggaggccagc
ctctccgtac ggcacccaga gtacaacaga ctcttgctcg ctaacgacct catgctcatc
aagttggacg aatccgtgtc cgagtctgac accatccgga gcatcagcat tgcttcgcag
tgccctaccg cggggaactc ttgcctcgtn tctggctggg gtctgctggc gaacggcaga
atgectaceg tgetgeactg egtgaaegtg teggtggtgt etgaggangt etgeagtaag
etetatgace egetgtacea ecceageatg ttetgegeeg geggagggea agaceagaag
gacteetgea aeggtgaete tggggggeee etgatetgea aegggtaett geagggeett
gtgtettteg gaaaageece gtgtggeeaa ettggegtge caggtgteta caecaacete
tgcaaattca ctgagtggat agagaaaacc gtccagncca gttaactctg gggactggga
acccatgaaa ttgaccccca aatacatcct gcggaangaa ttcaggaata tctgttccca
gecetteete ceteaggeee aggagteeag geceecagee cetecteeet caaaceaagg
gtacagatec ccagececte eteceteaga eccaggagte cagaecece ageceetent
centeagace caggagteca geceteete enteagacge aggagtecag acceeceage
cententeeq teagacecag gggtgeagge ceceaacece tenteentea gagteagagg
tecaageece caaceecteg ttececagae ceagaggtne aggteecage ceetecteec
                                                                      1020
tcagacccag cggtccaatg ccacctagan tntccctgta cacagtgccc ccttgtggca
                                                                      1080
ngttgaccca accttaccag ttggtttttc attttttgtc cctttcccct agatccagaa
                                                                      1140
                                                                      1167
ataaagtnta agagaagcgc aaaaaaa
      <210> 176
      <211> 205
      <212> PRT
      <213> Homo sapien
      <220>
      <221> VARIANT
      <222> (1)...(205)
      <223> Xaa = Any Amino Acid
      <400> 176
Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp
Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu
Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val
                            40
Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Leu Leu Leu
Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
                    70
                                        75
Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
                85
Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met
                                105
                                                    110
```

Pro Thr Val Leu His Cys Val Asn Val Ser Val Val Ser Glu Xaa Val

120 Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala

115

125

```
130
                        135
Gly Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly
                                        155
                    150
Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys
                                    170
                165
Ala Pro Cys Gly Gln Leu Gly Val Pro Gly Val Tyr Thr Asn Leu Cys
                                185
Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Xaa Ser
                                                 205
        195
                            200
      <210> 177
      <211> 1119
      <212> DNA
      <213> Homo sapien
      <400> 177
                                                                        60
qcqcactcqc agccctgqca ggcggcactg gtcatggaaa acgaattgtt ctgctcgggc
gtcctggtgc atccgcagtg ggtgctgtca gccgcacact gtttccagaa ctcctacacc
                                                                       120
atcgggctgg gcctgcacag tcttgaggcc gaccaagagc cagggagcca gatggtggag
                                                                       180
gccagcetet cegtaeggea eccagagtae aacagaeeet tgetegetaa egaeeteatg
                                                                       240
ctcatcaagt tggacgaatc cgtgtccgag tctgacacca tccggagcat cagcattgct
                                                                       300
tegeagtgee etacegeggg gaactettge etegtttetg getggggtet getggegaac
                                                                       360
                                                                       420
gatgctgtga ttgccatcca gtcccagact gtgggaggct gggagtgtga gaagctttcc
                                                                       480
caaccctggc agggttgtac cattteggca acttecagtg caaggacgtc ctgctgcatc
ctcactgggt getcactact getcactgca tcacceggaa cactgtgate aactagecag
                                                                       540
caccatagtt ctccgaagtc agactatcat gattactgtg ttgactgtgc tgtctattgt
                                                                       600
actaaccatg ccgatgttta ggtgaaatta gcgtcacttg gcctcaacca tcttggtatc
                                                                       660
cagttatect cactgaattg agattteetg etteagtgte agecatteee acataattte
                                                                       720
tqacctacaq aggtgaggga tcatatagct cttcaaggat gctggtactc ccctcacaaa
                                                                       780
ttcatttctc ctgttgtagt gaaaggtgcg ccctctggag cctcccaggg tgggtgtgca
                                                                       840
ggtcacaatg atgaatgtat gatcgtgttc ccattaccca aagcctttaa atccctcatg
                                                                       900
                                                                       960
ctcagtacac cagggcaggt ctagcatttc ttcatttagt gtatgctgtc cattcatgca
                                                                      1020
accaceteag gacteetgga ttetetgeet agttgagete etgeatgetg ceteettggg
gaggtgaggg agagggccca tggttcaatg ggatctgtgc agttgtaaca cattaggtgc
                                                                      1080
                                                                      1119
ttaataaaca gaagctgtga tgttaaaaaa aaaaaaaaa
      <210> 178
      <211> 164
      <212> PRT
      <213> Homo sapien
      <220>
      <221> VARIANT
      <222> (1)...(164)
      <223> Xaa = Any Amino Acid
      <400> 178
Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp
                                     10
```

Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu

25

30

20

```
Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val
                            40
                                                 45
Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu
Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
                                        75
Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Asp Ala Val
                                105
Ile Ala Ile Gln Ser Xaa Thr Val Gly Gly Trp Glu Cys Glu Lys Leu
                            120
                                                 125
        115
Ser Gln Pro Trp Gln Gly Cys Thr Ile Ser Ala Thr Ser Ser Ala Arg
                        135
Thr Ser Cys Cys Ile Leu Thr Gly Cys Ser Leu Leu Thr Ala Ser
145
                    150
                                        155
                                                             160
Pro Gly Thr Leu
      <210> 179
      <211> 250
      <212> DNA
      <213> Homo sapien
      <400> 179
ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct
                                                                        60
ccagctgccc ccggccgggg gatgcgaggc tcggagcacc cttgcccggc tgtgattgct
                                                                       120
gccaggcact gttcatctca gcttttctgt ccctttgctc ccggcaageg cttctgctga
                                                                       180
aagttcatat ctggagcctg atgtcttaac gaataaaggt cccatgctcc acccgaaaaa
                                                                       240
                                                                       250
aaaaaaaaa
      <210> 180
      <211> 202
      <212> DNA
      <213> Homo sapien
      <400> 180
actaqtccaq tqtqqtggaa ttccattqtg ttgggcccaa cacaatggct acctttaaca
                                                                        60
tcacccagac cccgcccctg cccgtgcccc acgctgctgc taacgacagt atgatgctta
                                                                       120
ctctgctact cggaaactat ttttatgtaa ttaatgtatg ctttcttgtt tataaatgcc
                                                                       180
tqatttaaaa aaaaaaaaaa aa
                                                                       202
      <210> 181
      <211> 558
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(558)
```

<223> n = A, T, C or G

```
<400> 181
tccytttgkt naggtttkkg agacamccck agacctwaan ctgtgtcaca gacttcyngg
                                                                        60
aatgtttagg cagtgctagt aatttcytcg taatgattct gttattactt tcctnattct
                                                                        120
ttattcctct ttcttctgaa gattaatgaa gttgaaaatt gaggtggata aatacaaaaa
                                                                       180
ggtagtgtga tagtataagt atctaagtgc agatgaaagt gtgttatata tatccattca
                                                                       240
aaattatgca agttagtaat tactcagggt taactaaatt actttaatat gctgttgaac
                                                                       300
ctactctgtt ccttggctag aaaaaattat aaacaggact ttgttagttt gggaagccaa
                                                                       360
attgataata ttctatgttc taaaagttgg gctatacata aattattaag aaatatggaw
                                                                       420
ttttattccc aggaatatgg kgttcatttt atgaatatta cscrggatag awqtwtqaqt
                                                                       480
aaaaycagtt ttggtwaata ygtwaatatg tcmtaaataa acaakgcttt gacttatttc
                                                                       540
caaaaaaaa aaaaaaaa
                                                                       558
      <210> 182
      <211> 479
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(479)
      <223> n = A, T, C or G
      <400> 182
acagggwttk grggatgcta agsccccrga rwtygtttga tccaaccctg gcttwttttc
                                                                        60
agaggggaaa atggggccta gaagttacag mscatytagy tggtgcgmtg gcacccctgg
                                                                       120
cstcacacag astcccgagt agctgggact acaggcacac agtcactgaa gcaggccctg
                                                                       180
ttwgcaattc acgttgccac ctccaactta aacattcttc atatgtgatg tccttagtca
                                                                       240
ctaaggttaa actttcccac ccagaaaagg caacttagat aaaatcttag agtactttca
                                                                       300
tactmttcta agtcctcttc cagcctcact kkgagtcctm cytgggggtt gataggaant
                                                                       360
ntctcttggc tttctcaata aartctctat ycatctcatg tttaatttgg tacgcatara
                                                                       420
awtgstgara aaattaaaat gttctggtty mactttaaaa araaaaaaaa aaaaaaaa
                                                                       479
      <210> 183
      <211> 384
      <212> DNA
      <213> Homo sapien
      <400> 183
aggegggage agaagetaaa gecaaageee aagaagagtg geagtgeeag caetggtgee
                                                                        60
agtaccagta ccaataacag tgccagtgcc agtgccagca ccagtggtgg cttcagtgct
                                                                       120
ggtgccagcc tgaccgccac tctcacattt gggctcttcg ctggccttgg tggagctggt
                                                                       180
gccagcacca gtggcagctc tggtgcctgt ggtttctcct acaagtgaga ttttagatat
                                                                       240
tgttaatcet gecagtettt etetteaage cagggtgeat eeteagaaae etaeteaaca
                                                                       300
cagcactcta ggcagccact atcaatcaat tgaagttgac actctgcatt aratctattt
                                                                       360
gccatttcaa aaaaaaaaaa aaaa
                                                                       384
      <210> 184
      <211> 496
      <212> DNA
```

```
<220>
      <221> misc feature
      <222> (1)...(496)
      <223> n = A, T, C \text{ or } G
      <400> 184
accgaattgg gaccgctggc ttataagcga tcatgtyynt ccrgtatkac ctcaacgagc
                                                                         60
agggagateg agtetataeg etgaagaaat ttgaceegat gggacaacag acetgeteag
                                                                        120
cccatcctgc tcggttctcc ccagatgaca aatactctsg acaccgaatc accatcaaga
                                                                        180
aacgettcaa ggtgetcatg acceagcaac egegeeetgt eetetgaggg teeettaaac
                                                                        240
tgatgtettt tetgecacet gttacecete ggagaeteeg taaccaaact etteggaetg
                                                                        300
tgagccctga tgcctttttg ccagccatac tctttggcat ccagtctctc gtggcgattg
                                                                        360
attatgcttg tgtgaggcaa tcatggtggc atcacccata aagggaacac atttgacttt
                                                                        420
tttttctcat attttaaatt actacmagaw tattwmagaw waaatgawtt gaaaaactst
                                                                        480
taaaaaaaa aaaaaa
                                                                        496
      <210> 185
      <211> 384
      <212> DNA
      <213> Homo sapien
      <400> 185
gctggtagcc tatggcgkgg cccacggagg ggctcctgag gccacggrac agtgacttcc
                                                                         60
caagtatcyt gcgcsgcgtc ttctaccgtc cctacctgca gatcttcggg cagattcccc
                                                                        120
aggaggacat ggacgtggcc ctcatggagc acagcaactg ytcgtcggag cccggcttct
                                                                        180
gggcacaccc tcctggggcc caggcgggca cctgcgtctc ccagtatgcc aactggctgg
                                                                        240
tggtgctgct cctcgtcatc ttcctgctcg tggccaacat cctgctggtc aacttgctca
                                                                        300
ttgccatgtt cagttacaca ttcggcaaag tacagggcaa cagcgatctc tactgggaag
                                                                        360
gcgcagcgtt accgcctcat ccgg
                                                                        384
      <210> 186
      <211> 577
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(577)
      <223> n = A,T,C \text{ or } G
      <400> 186
gagttagete etecacaace ttgatgaggt egtetgeagt ggeetetege tteatacege
                                                                         60
tnecategte atactgtagg tttgecacea cyteetggea tettggggeg gentaatatt
                                                                        120
ccaggaaact ctcaatcaag tcaccgtcga tgaaacctgt gggctggttc tgtcttccgc
                                                                        180
teggtgtgaa aggateteee agaaggagtg etegatette eecacaettt tgatgaettt
                                                                        240
attgagtcga ttctgcatgt ccagcaggag gttgtaccag ctctctgaca gtgaggtcac
                                                                        300
cagccctatc atgccgttga mcgtgccgaa garcaccgag ccttgtgtgg gggkkgaagt
                                                                        360
ctcacccaga ttctgcatta ccagagagcc gtggcaaaag acattgacaa actcgcccag
                                                                        420
gtggaaaaag amcamcteet ggargtgetn geegeteete gtemgttggt ggeagegetw
                                                                        480
tecttttgac acacaaacaa gttaaaggca ttttcagccc ccagaaantt gtcatcatcc
                                                                        540
```

```
577
aagatntcgc acagcactna tccagttggg attaaat
     <210> 187
      <211> 534
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(534)
      <223> n = A,T,C or G
      <400> 187
aacatcttcc tgtataatgc tgtgtaatat cgatccgatn ttgtctgstg agaatycatw
                                                                        60
actkggaaaa gmaacattaa agcctggaca ctggtattaa aattcacaat atgcaacact
                                                                       120
ttaaacagtg tgtcaatctg ctcccyynac tttgtcatca ccagtctggg aakaagggta
                                                                       180
tgccctattc acacctgtta aaagggcgct aagcattttt gattcaacat cttttttttt
                                                                       240
gacacaagtc cgaaaaaagc aaaagtaaac agttatyaat ttgttagcca attcactttc
                                                                       300
ttcatgggac agagccatyt gatttaaaaa gcaaattgca taatattgag cttygggagc
                                                                       360
tgatatttga geggaagagt ageettteta etteaceaga cacaacteec ttteatattg
                                                                       420
qqatqttnac naaaqtwatg tctctwacag atgggatgct tttgtggcaa ttctgttctg
                                                                       480
aggatetece agtttattta ecaettgeae aagaaggegt tttetteete agge
                                                                       534
      <210> 188
     <211> 761
      <212> DNA
     <213> Homo sapien
     <220>
      <221> misc feature
     <222> (1)...(761)
      <223> n = A,T,C or G
      <400> 188
agaaaccagt atctctnaaa acaacctctc ataccttgtg gacctaattt tgtgtgcgtg
                                                                        60
tqtqtqtqcq cqcatattat atagacaggc acatcttttt tacttttqta aaaqcttatq
                                                                       120
cctctttggt atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct
                                                                       180
ttgtcttctg tgtaaatggt actagagaaa acacctatnt tatgagtcaa tctagttngt
                                                                       240
tttattcgac atgaaggaaa tttccagatn acaacactna caaactctcc ctkgackarg
                                                                       300
ggggacaaag aaaagcaaaa ctgamcataa raaacaatwa cctggtgaga arttgcataa
                                                                       360
acagaaatwr ggtagtatat tgaarnacag catcattaaa rmgttwtktt wttctccctt
                                                                       420
qcaaaaaaaa tqtacnqact tcccqttqaq taatqccaaq ttqttttttt tatnataaaa
                                                                       480
cttgcccttc attacatgtt tnaaagtggt gtggtgggcc aaaatattga aatgatggaa
                                                                       540
ctgactgata aagctgtaca aataagcagt gtgcctaaca agcaacacag taatgttgac
                                                                       600
atgcttaatt cacaaatgct aatttcatta taaatgtttg ctaaaataca ctttgaacta
                                                                       660
tttttctgtn ttcccagagc tgagatntta gattttatgt agtatnaagt gaaaaantac
                                                                       720
gaaaataata acattgaaga aaaananaaa aaanaaaaaa a
                                                                       761
      <210> 189
      <211> 482
```

```
<213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(482)
      <223> n = A,T,C \text{ or } G
      <400> 189
tttttttttt tttgccgatn ctactatttt attgcaggan gtgggggtgt atgcaccgca
                                                                         60
caccggggct atnagaagca agaaggaagg agggagggca cagccccttg ctgagcaaca
                                                                        120
aageegeetg etgeettete tgtetgtete etggtgeagg cacatgggga gacetteece
                                                                        180
aaggcagggg ccaccagtcc aggggtggga atacaggggg tgggangtgt gcataagaag
                                                                        240
tgataggcac aggccacccg gtacagaccc ctcggctcct gacaggtnga tttcgaccag
                                                                        300
gtcattgtgc cctgcccagg cacagcgtan atctggaaaa gacagaatgc tttccttttc
                                                                        360
aaatttggct ngtcatngaa ngggcanttt tccaanttng gctnggtctt ggtacncttg
                                                                        420
gtteggeeca geteenegte caaaaantat teaccennet eenaattget tgenggneec
                                                                        480
CC
                                                                        482
      <210> 190
      <211> 471
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(471)
      <223> n = A, T, C \text{ or } G
      <400> 190
tttttttttt ttttaaaaca gtttttcaca acaaaattta ttagaagaat agtggttttg
                                                                         60
aaaactctcg catccagtga gaactaccat acaccacatt acagctngga atgtnctcca
                                                                        120
aatgtctggt caaatgatac aatggaacca ttcaatctta cacatgcacg aaagaacaag
                                                                        180
cgcttttgac atacaatgca caaaaaaaaa agggggggg gaccacatgg attaaaattt
                                                                        240
taagtactca tcacatacat taagacacag ttctagtcca gtcnaaaatc agaactgcnt
                                                                        300
tgaaaaattt catgtatgca atccaaccaa agaacttnat tggtgatcat gantnctcta
                                                                        360
ctacatcnac cttgatcatt gccaggaacn aaaagttnaa ancacncngt acaaaaanaa
                                                                        420
tctgtaattn anttcaacct ccgtacngaa aaatnttnnt tatacactcc c
                                                                        471
      <210> 191
      <211> 402
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (402)
      <223> n = A,T,C or G
      <400> 191
gagggattga aggtctgttc tastgtcggm ctgttcagcc accaactcta acaagttgct
                                                                         60
gtcttccact cactgtctgt aagcttttta acccagacwg tatcttcata aatagaacaa
                                                                        120
```

```
180
attottcacc agtcacatct totaggacct ttttggattc agttagtata agctcttcca
cttcctttgt taagacttca tctggtaaag tcttaagttt tgtagaaagg aattyaattg
                                                                        240
                                                                        300
ctcqttctct aacaatgtcc tctccttgaa gtatttggct gaacaaccca cctaaagtcc
                                                                        360
ctttgtgcat ccattttaaa tatacttaat agggcattgk tncactaggt taaattctgc
                                                                        402
aagagtcatc tgtctgcaaa agttgcgtta gtatatctgc ca
      <210> 192
      <211> 601
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(601)
      <223> n = A,T,C \text{ or } G
      <400> 192
                                                                         60
qaqctcggat ccaataatct ttgtctgagg gcagcacaca tatncagtgc catggnaact
ggtctacccc acatgggagc agcatgccgt agntatataa ggtcattccc tgagtcagac
                                                                        120
atgcytyttt gaytaccgtg tgccaagtgc tggtgattct yaacacacyt ccatcccgyt
                                                                        180
                                                                        240
cttttgtgga aaaactggca cttktctgga actagcarga catcacttac aaattcaccc
                                                                        300
acgagacact tgaaaggtgt aacaaagcga ytcttgcatt gctttttgtc cctccggcac
cagttgtcaa tactaacccg ctggtttgcc tccatcacat ttgtgatctg tagctctgga
                                                                        360
tacatctcct gacagtactg aagaacttct tcttttgttt caaaagcarc tcttggtgcc
                                                                        420
tgttggatca ggttcccatt tcccagtcyg aatgttcaca tggcatattt wacttcccac
                                                                        480
aaaacattgc gatttgaggc tcagcaacag caaatcctgt tccggcattg gctgcaagag
                                                                        540
                                                                        600
cctcgatgta gccggccagc gccaaggcag gcgccgtgag ccccaccagc agcagaagca
                                                                        601
      <210> 193
      <211> 608
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(608)
      \langle 223 \rangle n = A,T,C or G
      <400> 193
                                                                         60
atacageeca nateecaeca egaagatgeg ettgttgaet gagaacetga tgeggteaet
                                                                        120
ggtcccgctg tagccccagc gactctccac ctgctggaag cggttgatgc tgcactcytt
                                                                        180
cccaacgcag gcagmagcgg gsccggtcaa tgaactccay tcgtggcttg gggtkgacgg
tkaagtgcag gaagaggctg accacctcgc ggtccaccag gatgcccgac tgtgcgggac
                                                                        240
                                                                        300
ctgcagcgaa actcctcgat ggtcatgagc gggaagcgaa tgaggcccag ggccttgccc
                                                                        360
agaacettee geetgttete tggegteace tgeagetget geegetgaca eteggeeteg
                                                                        420
gaccagegga caaacggert tgaacageeg caceteaegg atgeecagtg tgtegegete
                                                                        480
caggammgsc accagegtgt ccaggtcaat gteggtgaag cccteegegg gtratggegt
ctgcagtgtt tttgtcgatg ttctccaggc acaggctggc cagctgcggt tcatcgaaga
                                                                        540
                                                                        600
gtegegeetg egtgageage atgaaggegt tgteggeteg eagttettet teaggaacte
                                                                        608
cacgcaat
```

```
<210> 194
      <211> 392
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(392)
      <223> n = A, T, C \text{ or } G
      <400> 194
qaacqqctqq accttgcctc gcattgtgct tgctggcagg gaataccttg gcaagcagyt
                                                                         60
ccaqtccqag cagccccaga ccgctgccgc ccgaagctaa gcctgcctct ggccttcccc
                                                                        120
tccqcctcaa tgcagaacca gtagtgggag cactgtgttt agagttaaga gtgaacactg
                                                                        180
tttqatttta cttgggaatt tcctctgtta tatagctttt cccaatgcta atttccaaac
                                                                        240
                                                                        300
aacaacaaca aaataacatg tttgcctgtt aagttgtata aaagtaggtg attctgtatt
taaagaaaat attactgtta catatactgc ttgcaatttc tgtatttatt gktnctstgg
                                                                        360
                                                                        392
aaataaatat agttattaaa ggttgtcant cc
      <210> 195
      <211> 502
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(502)
      <223> n = A, T, C \text{ or } G
      <400> 195
ccsttkgagg ggtkaggkyc cagttyccga gtggaagaaa caggccagga gaagtgcgtg
                                                                         60
                                                                        120
ccgagctgag gcagatgttc ccacagtgac ccccagagcc stgggstata gtytctgacc
cctcncaagg aaagaccacs ttctggggac atgggctgga gggcaggacc tagaggcacc
                                                                        180
                                                                        240
aagggaaggc cccattccgg ggstgttccc cgaggaggaa gggaagggc tctgtgtgcc
ccccasgagg aagaggccct gagtcctggg atcagacacc ccttcacgtg tatccccaca
                                                                        300
caaatqcaaq ctcaccaagg tcccctctca gtccccttcc stacaccctg amcggccact
                                                                        360
qscscacacc cacccagagc acgccacccg ccatggggar tgtgctcaag gartegengg
                                                                        420
gcarcgtgga catcingtcc cagaaggggg cagaatctcc aatagangga cigarcmstt
                                                                        480
gctnanaaaa aaaaanaaaa aa
                                                                        502
      <210> 196
      <211> 665
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(665)
      <223> n = A, T, C or G
```

```
<400> 196
ggttacttgg tttcattgcc accacttagt ggatgtcatt tagaaccatt ttgtctgctc
                                                                         60
cctctqqaaq ccttqcqcaq agcggacttt gtaattgttg gagaataact gctgaatttt
                                                                        120
wagctgtttk gagttgatts gcaccactgc acccacaact tcaatatgaa aacyawttga
                                                                        180
actwatttat tatcttgtga aaagtataac aatgaaaatt ttgttcatac tgtattkatc
                                                                        240
aagtatgatg aaaagcaawa gatatatatt cttttattat gttaaattat gattgccatt
                                                                        300
attaatcogc aaaatotoga ototatottc ttttcacagt aatatatocc ttttgtaact
                                                                        360
tcacttggtt attttattgt aaatgartta caaaattctt aatttaagar aatggtatgt
                                                                        420
watatttatt tcattaattt ctttcctkgt ttacgtwaat tttgaaaaga wtgcatgatt
                                                                        480
tettgacaga aategatett gatgetgtgg aagtagtttg acceacatee etatgagttt
                                                                        540
ttottagaat gtataaaggt tgtagoocat cnaacttcaa agaaaaaaat gaccacatac
                                                                        600
tttgcaatca ggctgaaatg tggcatgctn ttctaattcc aactttataa actagcaaan
                                                                        660
                                                                        665
aagtg
      <210> 197
      <211> 492
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(492)
      <223> n = A, T, C \text{ or } G
      <400> 197
ttttnttttt tttttttgc aggaaggatt ccatttattg tggatgcatt ttcacaatat
                                                                         60
atgtttattg gagcgatcca ttatcagtga aaagtatcaa gtgtttataa natttttagg
                                                                        120
aaqqcaqatt cacaqaacat gctngtcngc ttgcagtttt acctcgtana gatnacagag
                                                                        180
aattatagtc naaccagtaa acnaggaatt tacttttcaa aagattaaat ccaaactgaa
                                                                        240
caaaattcta ccctqaaact tactccatcc aaatattgga ataanagtca gcagtgatac
                                                                        300
attetettet gaactttaga tittetagaa aaatatgtaa tagtgateag gaagagetet
                                                                        360
tqttcaaaaq tacaacnaaq caatgttccc ttaccatagg ccttaattca aactttgatc
                                                                        420
cattleacte ceateaeggg agteaatget acctgggaca cttgtatttt gtteatnetg
                                                                        480
                                                                        492
ancntggctt aa
      <210> 198
      <211> 478
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(478)
      <223> n = A, T, C \text{ or } G
      <400> 198
tttnttttgn atttcantct gtannaanta ttttcattat gtttattana aaaatatnaa
                                                                         60
tqtntccacn acaaatcatn ttacntnagt aagaggccan ctacattgta caacatacac
                                                                        120
tqaqtatatt ttgaaaagga caagtttaaa gtanacncat attgccganc atancacatt
                                                                        180
tatacatggc ttgattgata tttagcacag canaaactga gtgagttacc agaaanaaat
                                                                        240
natatatgtc aatcngattt aagatacaaa acagatccta tggtacatan catcntgtag
                                                                        300
```

```
360
gagttgtggc tttatgttta ctgaaagtca atgcagttcc tgtacaaaga gatggccgta
                                                                         420
agcattctag tacctctact ccatggttaa gaatcgtaca cttatgttta catatgtnca
gggtaagaat tgtgttaagt naanttatgg agaggtccan gagaaaaatt tgatncaa
                                                                        478
      <210> 199
      <211> 482
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(482)
      <223> n = A,T,C \text{ or } G
      <400> 199
agtgacttgt cctccaacaa aaccccttga tcaagtttgt ggcactgaca atcagaccta
                                                                         60
                                                                         120
tqctaqttcc tgtcatctat tcgctactaa atgcagactg gaggggacca aaaaggggca
                                                                         180
tcaactccag ctggattatt ttggagcctg caaatctatt cctacttgta cggactttga
agtgattcag tttcctctac ggatgagaga ctggctcaag aatatcctca tgcagcttta
                                                                         240
                                                                         300
tqaaqccnac tctgaacacg ctggttatct nagatgagaa ncagagaaat aaagtcnaga
aaatttacct ggangaaaag aggctttngg ctggggacca tcccattgaa ccttctctta
                                                                         360
anggacttta agaanaaact accacatgtn tgtngtatcc tggtgccngg ccgtttantg
                                                                         420
aacntngacn ncaccettnt ggaatanant ettgaengen teetgaaett geteetetge
                                                                         480
                                                                         482
ga
      <210> 200
      <211> 270
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (270)
      <223> n = A, T, C or G
      <400> 200
                                                                          60
cgqccqcaaq tgcaactcca gctggggccg tgcggacgaa gattctgcca gcagttggtc
cgactgcgac gacggcggcg gcgacagtcg caggtgcagc gcgggcgcct ggggtcttgc
                                                                         120
aaggetgage tgaegeegea gaggtegtgt caegteecae gaeettgaeg eegtegggga
                                                                         180
cagccggaac agagcccggt gaangcggga ggcctcgggg agcccctcgg gaagggcggc
                                                                         240
ccgagagata cgcaggtgca ggtggccgcc
                                                                         270
      <210> 201
      <211> 419
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(419)
      <223> n = A, T, C \text{ or } G
```

```
<400> 201
tttttttttt ttttggaatc tactgcgagc acagcaggtc agcaacaagt ttattttgca
                                                                       60
gctagcaagg taacagggta gggcatggtt acatgttcag gtcaacttcc tttgtcgtgg
                                                                      120
ttgattggtt tgtctttatg ggggcggggt ggggtagggg aaancgaagc anaantaaca
                                                                      180
                                                                      240
tggagtgggt gcacctccc tgtagaacct ggttacnaaa gcttggggca gttcacctgg
                                                                      300
totqtqaccq toattttott gacatcaatg ttattagaag toaggatato ttttagagag
tccactgtnt ctggagggag attagggttt cttgccaana tccaancaaa atccacntga
                                                                      360
aaaaqttqqa tqatncangt acngaatacc ganggcatan ttctcatant cggtggcca
                                                                      419
      <210> 202
      <211> 509
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(509)
      <223> n = A, T, C \text{ or } G
      <400> 202
tttnttttt tttttttt tttttttt tttttttt
                                                                       60
tggcacttaa tccattttta tttcaaaatg tctacaaant ttnaatncnc cattatacng
                                                                      120
qtnattttnc aaaatctaaa nnttattcaa atntnagcca aantccttac ncaaatnnaa
                                                                      180
tacncncaaa aatcaaaaat atacntntct ttcagcaaac ttngttacat aaattaaaaa
                                                                      240
aatatatacq gctggtgttt tcaaagtaca attatcttaa cactgcaaac atntttnnaa
                                                                      300
ggaactaaaa taaaaaaaaa cactneegea aaggttaaag ggaacaacaa attentttta
                                                                      360
caacancnnc nattataaaa atcatatctc aaatcttagg ggaatatata cttcacacng
                                                                      420
ggatcttaac ttttactnca ctttgtttat ttttttanaa ccattgtntt gggcccaaca
                                                                      480
caatggnaat nccnccncnc tggactagt
                                                                       509
      <210> 203
      <211> 583
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (583)
      <223> n = A,T,C or G
      <400> 203
                                                                        60
ttttttttt tttttttga ccccctctt ataaaaaaca agttaccatt ttattttact
tacacatatt tattttataa ttggtattag atattcaaaa ggcagctttt aaaaatcaaac
                                                                       120
taaatggaaa ctgccttaga tacataattc ttaggaatta gcttaaaatc tgcctaaagt
                                                                       180
gaaaatcttc tctagctctt ttgactgtaa atttttgact cttgtaaaac atccaaattc
                                                                       240
atttttcttg tctttaaaat tatctaatct ttccattttt tccctattcc aagtcaattt
                                                                       300
gcttctctag cctcatttcc tagctcttat ctactattag taagtggctt ttttcctaaa
                                                                       360
agggaaaaca ggaagagana atggcacaca aaacaaacat tttatattca tatttctacc
                                                                       420
tacgttaata aaatagcatt ttgtgaagcc agctcaaaag aaggcttaga tccttttatg
                                                                       480
tccattttag tcactaaacg atatcnaaag tgccagaatg caaaaggttt gtgaacattt
                                                                       540
```

```
583
attcaaaagc taatataaga tatttcacat actcatcttt ctg
      <210> 204
      <211> 589
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(589)
      <223> n = A, T, C or G
      <400> 204
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                                                                        60
tttcactctc tagatagggc atgaagaaaa ctcatctttc cagctttaaa ataacaatca
                                                                       120
aatctcttat gctatatcat attttaagtt aaactaatga gtcactggct tatcttctcc
                                                                       180
tgaaggaaat ctgttcattc ttctcattca tatagttata tcaagtacta ccttgcatat
                                                                       240
tgagaggttt ttcttctcta tttacacata tatttccatg tgaatttgta tcaaaccttt
                                                                       300
attttcatgc aaactagaaa ataatgtntt cttttgcata agagaagaga acaatatnag
                                                                       360
cattacaaaa ctgctcaaat tgtttgttaa gnttatccat tataattagt tnggcaggag
                                                                       420
ctaatacaaa tcacatttac ngacnagcaa taataaaact gaagtaccag ttaaatatcc
                                                                       480
aaaataatta aaggaacatt tttagcctgg gtataattag ctaattcact ttacaagcat
                                                                       540
ttattnagaa tgaattcaca tgttattatt ccntagccca acacaatgg
                                                                       589
      <210> 205
      <211> 545
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(545)
      <223> n = A,T,C or G
      <400> 205
tttttntttt tttttcagt aataatcaga acaatattta tttttatatt taaaattcat
                                                                        60
aqaaaaqtgc cttacattta ataaaagttt gtttctcaaa gtgatcagag gaattagata
                                                                       120
tngtcttgaa caccaatatt aatttgagga aaatacacca aaatacatta agtaaattat
                                                                       180
ttaagatcat agagcttgta agtgaaaaga taaaatttga cctcagaaac tctgagcatt
                                                                       240
aaaaatccac tattaqcaaa taaattacta tggacttctt gctttaattt tgtgatgaat
                                                                       300
atggggtgtc actggtaaac caacacattc tgaaggatac attacttagt gatagattct
                                                                       360
tatqtacttt qctanatnac gtggatatga gttgacaagt ttctctttct tcaatctttt
                                                                       420
aaqqqqcnqa nqaaatgagq aagaaaagaa aaggattacg catactgttc tttctatngg
                                                                       480
aaqqattaqa tatqtttcct ttgccaatat taaaaaaata ataatgttta ctactagtga
                                                                       540
                                                                       545
aaccc
      <210> 206
      <211> 487
      <212> DNA
```

```
<220>
      <221> misc feature
      <222> (1)...(487)
      <223> n = A, T, C \text{ or } G
      <400> 206
                                                                         60
ttttttttt ttttttagtc aagtttctna tttttattat aattaaagtc ttggtcattt
                                                                        120
catttattag ctctgcaact tacatattta aattaaagaa acgttnttag acaactgtna
caatttataa atgtaaggtg ccattattga gtanatatat tcctccaaga gtggatgtgt
                                                                        180
cccttctccc accaactaat gaancagcaa cattagttta attttattag tagatnatac
                                                                        240
                                                                        300
actgctgcaa acgctaattc tcttctccat ccccatgtng atattgtgta tatgtgtgag
ttggtnagaa tgcatcanca atctnacaat caacagcaag atgaagctag gcntgggctt
                                                                        360
                                                                        420
teggtgaaaa tagactgtgt etgtetgaat caaatgatet gacetateet eggtggeaag
aactettega accgetteet caaaggenge tgecacattt gtggentetn ttgeaettgt
                                                                        480
                                                                        487
ttcaaaa
      <210> 207
      <211> 332
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(332)
      <223> n = A,T,C or G
      <400> 207
tgaattggct aaaagactgc atttttanaa ctagcaactc ttatttcttt cctttaaaaa
                                                                         60
                                                                        120
tacatagcat taaatcccaa atcctattta aagacctgac agcttgagaa ggtcactact
gcatttatag gaccttctgg tggttctgct gttacntttg aantctgaca atccttgana
                                                                        180
atctttgcat gcagaggagg taaaaggtat tggattttca cagaggaana acacagcgca
                                                                        240
gaaatgaagg ggccaggctt actgagcttg tccactggag ggctcatggg tgggacatgg
                                                                        300
                                                                        332
aaaagaaggc agcctaggcc ctggggagcc ca
       <210> 208
       <211> 524
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(524)
       <223> n = A, T, C or G
       <400> 208
                                                                          60
 agggcgtggt gcggagggcg ttactgtttt gtctcagtaa caataaatac aaaaagactg
 gttgtgttcc ggccccatcc aaccacgaag ttgatttctc ttgtgtgcag agtgactgat
                                                                         120
                                                                         180
 tttaaaggac atggagcttg tcacaatgtc acaatgtcac agtgtgaagg gcacactcac
 tecegegtga tteacattta geaaceaaca atageteatg agtecataet tgtaaataet
                                                                         240
 tttggcagaa tacttnttga aacttgcaga tgataactaa gatccaagat atttcccaaa
                                                                         300
 gtaaatagaa gtgggtcata atattaatta cctgttcaca tcagcttcca tttacaagtc
                                                                         360
```

```
atgageceag acaetgaeat caaactaage ceaettagae teeteaceae cagtetgtee
                                                                        420
tgtcatcaga caggaggctg tcaccttgac caaattctca ccagtcaatc atctatccaa
                                                                        480
aaaccattac ctgatccact tccggtaatg caccaccttg gtga
                                                                        524
      <210> 209
      <211> 159
      <212> DNA
      <213> Homo sapien
      <400> 209
gggtgaggaa atccagagtt gccatggaga aaattccagt gtcagcattc ttgctccttg
                                                                         60
tgqccctctc ctacactctq gccagagata ccacagtcaa acctggagcc aaaaaggaca
                                                                        120
caaaggactc tcgacccaaa ctgccccaga ccctctcca
                                                                        159
      <210> 210
      <211> 256
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(256)
      \langle 223 \rangle n = A,T,C or G
      <400> 210
                                                                         60
actecetgge agacaaagge agaggagaga getetgttag ttetgtgttg ttgaactgee
actgaatttc tttccacttg gactattaca tgccanttga gggactaatg gaaaaacgta
                                                                        120
                                                                        180
tggggagatt ttanccaatt tangtntgta aatggggaga ctggggcagg cgggagagat
ttgcagggtg naaatgggan ggctggtttg ttanatgaac agggacatag gaggtaggca
                                                                        240
ccaggatgct aaatca
                                                                        256
      <210> 211
      <211> 264
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(264)
      <223> n = A, T, C \text{ or } G
      <400> 211
acattgtttt tttgagataa agcattgaga gagctctcct taacgtgaca caatggaagg
                                                                          60
actggaacac atacccacat ctttgttctg agggataatt ttctgataaa gtcttgctgt
                                                                         120
atattcaagc acatatgtta tatattattc agttccatgt ttatagccta gttaaggaga
                                                                        180
ggggagatac attcngaaag aggactgaaa gaaatactca agtnggaaaa cagaaaaaga
                                                                         240
aaaaaaggag caaatgagaa gcct
                                                                        264
      <210> 212
      <211> 328
```

```
<213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(328)
      <223> n = A,T,C or G
      <400> 212
acccaaaaat ccaatgctga atatttggct tcattattcc canattcttt gattgtcaaa
                                                                         60
ggatttaatg ttgtctcagc ttgggcactt cagttaggac ctaaggatgc cagccggcag
                                                                        120
gtttatatat gcagcaacaa tattcaagcg cgacaacagg ttattgaact tgcccgccag
                                                                        180
ttnaatttca ttcccattga cttgggatcc ttatcatcag ccagagagat tgaaaattta
                                                                        240
cccctacnac tetttactet etgganaggg ccagtggtgg tagetataag ettggccaca
                                                                        300
                                                                        328
ttttttttc ctttattcct ttgtcaga
      <210> 213
      <211> 250
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(250)
      <223> n = A, T, C or G
      <400> 213
                                                                         60
acttatgage agagegacat atcenagtgt agactgaata aaactgaatt etetecagtt
taaagcattg ctcactgaag ggatagaagt gactgccagg agggaaagta agccaaggct
                                                                        120
cattatgcca aagganatat acatttcaat tctccaaact tcttcctcat tccaagagtt
                                                                        180
ttcaatattt gcatgaacct gctgataanc catgttaana aacaaatatc tctctnacct
                                                                        240
                                                                        250
tctcatcggt
       <210> 214
       <211> 444
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(444)
       <223> n = A, T, C \text{ or } G
       <400> 214
 acccagaatc caatgotgaa tatttggott cattattocc agattotttg attgtcaaag
                                                                         60
 gatttaatgt tgtctcagct tgggcacttc agttaggacc taaggatgcc agccggcagg
                                                                         120
 tttatatatg cagcaacaat attcaagcgc gacaacaggt tattgaactt gcccgccagt
                                                                         180
 tgaatttcat tcccattgac ttgggatcct tatcatcagc canagagatt gaaaatttac
                                                                         240
 ccctacgact ctttactctc tggagagggc cagtggtggt agctataagc ttggccacat
                                                                         300
 ttttttttcc tttattcctt tgtcagagat gcgattcatc catatgctan aaaccaacag
                                                                         360
                                                                         420
 agtgactttt acaaaattcc tataganatt gtgaataaaa ccttacctat agttgccatt
                                                                         444
 actttgctct ccctaatata cctc
```

```
<210> 215
      <211> 366
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(366)
      <223> n = A,T,C or G
      <400> 215
                                                                         60
acttatqagc agagcgacat atccaagtgt anactgaata aaactgaatt ctctccagtt
taaagcattg ctcactgaag ggatagaagt gactgccagg agggaaagta agccaaggct
                                                                        120
cattatgcca aagganatat acatttcaat tetecaaact tetteetcat tecaagagtt
                                                                        180
ttcaatattt gcatgaacct gctgataagc catgttgaga aacaaatatc tctctgacct
                                                                        240
                                                                        300
tctcatcqqt aagcagaggc tgtaggcaac atggaccata gcgaanaaaa aacttagtaa
                                                                        360
tccaagctgt tttctacact gtaaccaggt ttccaaccaa ggtggaaatc tcctatactt
                                                                        366
ggtgcc
      <210> 216
      <211> 260
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(260)
      \langle 223 \rangle n = A,T,C or G
      <400> 216
                                                                         60
ctgtataaac agaactccac tgcangaggg agggccgggc caggagaatc tccgcttgtc
caagacaggg gcctaaggag ggtctccaca ctgctnntaa gggctnttnc attttttat
                                                                        120
taataaaaaq tnnaaaaggc etetteteaa etttttteee ttnggetgga aaatttaaaa
                                                                        180
atcaaaaatt tootnaagtt ntoaagotat catatatact ntatootgaa aaagoaacat
                                                                        240
                                                                        260
aattcttcct tccctccttt
      <210> 217
      <211> 262
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(262)
      <223> n = A,T,C or G
      <400> 217
acctacqtgg gtaagtttan aaatgttata atttcaggaa naggaacgca tataattgta
                                                                         60
tettgeetat aattitetat titaataagg aaatageaaa tiggggtggg gggaatgtag
                                                                        120
                                                                        180
ggcattctac agtttgagca aaatgcaatt aaatgtggaa ggacagcact gaaaaatttt
```

atgaataatc tgtatgatta tatgtctcta atatccttca tgcttgtaaa gt	gagtagattt	ataattagcc	acttacccta	240 262
<210> 218 <211> 205 <212> DNA <213> Homo sapien				
<220> <221> misc_feature <222> (1)(205) <223> n = A,T,C or G				
<pre>&lt;400&gt; 218 accaaggtgg tgcattaccg gaantggatc cccctatcaa ctcccttttg tagtaaactt aggcctcccc agttctactg acctttgtcc anaaatcagc agacacaggt gtaaa</pre>	ggaaccttgg	aaatgaccag	gccaagactc	60 120 180 205
<210> 219 <211> 114 <212> DNA <213> Homo sapien				
<400> 219 tactgttttg tctcagtaac aataaataca accacgaagt tgatttctct tgtgtgcaga			_	60 114
<210> 220 <211> 93 <212> DNA <213> Homo sapien				
<400> 220				
actagccage acaaaaggca gggtagcctg aaataagcat ttagtgetca gteectactg		tgctctttac	atttctttta	60 93
<210> 221 <211> 167 <212> DNA <213> Homo sapien				
<220> <221> misc_feature <222> (1)(167) <223> n = A,T,C or G				
<400> 221	1 1 1 2 - 1			
actangtgca ggtgcgcaca aatatttgtc tcttttgccc agcctgtggc tctactgtag	taagtttctg	ctgatgagga		60 120 167

```
<210> 222
      <211> 351
      <212> DNA
      <213> Homo sapien
      <400> 222
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                                                                         60
qttcttcacc tgtcccccaa tccttaaaag gccatactgc ataaagtcaa caacagataa
                                                                        120
atgtttgctg aattaaagga tggatgaaaa aaattaataa tgaatttttg cataatccaa
                                                                        180
                                                                        240
ttttctcttt tatatttcta gaagaagttt ctttgagcct attagatccc gggaatcttt
                                                                        300
taqqtqaqca tqattaqaga gcttgtaggt tgcttttaca tatatctggc atatttgagt
ctcqtatcaa aacaatagat tggtaaaggt ggtattattg tattgataag t
                                                                        351
      <210> 223
      <211> 383
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (383)
      \langle 223 \rangle n = A,T,C or G
      <400> 223
aaaacaaaca aacaaaaaa acaattcttc attcaqaaaa attatcttag ggactgatat
                                                                         60
tqqtaattat qqtcaattta atwrtrttkt ggggcatttc cttacattgt cttgacaaga
                                                                        120
ttaaaatgtc tgtgccaaaa ttttgtattt tatttggaga cttcttatca aaagtaatgc
                                                                        180
tgccaaagga agtctaagga attagtagtg ttcccmtcac ttgtttggag tgtgctattc
                                                                        240
taaaagattt tgatttcctg gaatgacaat tatattttaa ctttggtggg ggaaanagtt
                                                                        300
ataggaecae agtetteaet tetgataett gtaaattaat ettttattge aettgttttg
                                                                        360
                                                                        383
accattaagc tatatgttta aaa
      <210> 224
      <211> 320
      <212> DNA
      <213> Homo sapien
      <400> 224
cccctgaagg cttcttgtta gaaaatagta cagttacaac caataggaac aacaaaaaga
                                                                         60
aaaaqtttgt qacattqtag tagggagtgt gtacccctta ctccccatca aaaaaaaaat
                                                                        120
ggatacatgg ttaaaggata raagggcaat attttatcat atgttctaaa agagaaggaa
                                                                        180
gagaaaatac tactttctcr aaatggaagc ccttaaaggt gctttgatac tgaaggacac
                                                                        240
aaatgtggcc gtccatcctc ctttaragtt gcatgacttg gacacggtaa ctgttgcagt
                                                                        300
                                                                        320
tttaractcm gcattgtgac
      <210> 225
      <211> 1214
      <212> DNA
      <213> Homo sapien
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<400> 225
gaggaetgea geeegeacte geageeetgg caggeggeae tggteatgga aaacgaattg
                                                                      60
                                                                     120
ttctgctcgg gcgtcctggt gcatccgcag tgggtgctgt cagccgcaca ctgtttccag
aacteetaca ceateggget gggeetgeae agtettgagg eegaceaaga geeagggage
                                                                     180
cagatggtgg aggccagcct ctccgtacgg cacccagagt acaacagacc cttgctcgct
                                                                     240
aacgacetca tgeteateaa gttggaegaa teegtgteeg agtetgaeae cateeggage
                                                                     300
                                                                     360
atcagcattg cttcgcagtg ccctaccgcg gggaactctt gcctcgtttc tggctggggt
ctgctggcga acggcagaat gcctaccgtg ctgcagtgcg tgaacgtgtc ggtggtgtct
                                                                     420
                                                                     480
gaggaggtet geagtaaget etatgaeeeg etgtaeeaee eeageatgtt etgegeegge
ggagggcaag accagaagga ctcctgcaac ggtgactctg gggggcccct gatctgcaac
                                                                     540
                                                                     600
gggtacttgc agggccttgt gtctttcgga aaagccccgt gtggccaagt tggcgtgcca
                                                                     660
qqtqtctaca ccaacctctg caaattcact gagtggatag agaaaaccgt ccaggccagt
                                                                     720
taactctggg gactgggaac ccatgaaatt gacccccaaa tacatcctgc ggaaggaatt
caggaatate tgttcccage cectectece teaggeccag gagtccagge ceceagecee
                                                                     780
                                                                     840
tecteetea aaccaagggt acagateece ageceeteet eeeteagace caggagteea
                                                                     900
qacccccag ccctcctcc ctcagaccca ggagtccagc ccctcctcc tcagacccag
                                                                     960
gagtccagac ccccagccc ctcctccctc agacccaggg gtccaggccc ccaacccctc
                                                                    1020
ctccctcaga ctcagaggtc caagccccca acccctcctt ccccagaccc agaggtccag
qteccagece etectecete agacccageg gtecaatgee acetagaete tecetgtaca
                                                                    1080
cagtgcccc ttgtggcacg ttgacccaac cttaccagtt ggtttttcat tttttgtccc
                                                                    1140
1200
                                                                    1214
aaaaaaaaa aaaa
     <210> 226
     <211> 119
     <212> DNA
     <213> Homo sapien
     <400> 226
accoagtatg tgcagggaga cggaacccca tgtgacagcc cactccacca gggttcccaa
                                                                      60
agaacctggc ccagtcataa tcattcatcc tgacagtggc aataatcacg ataaccagt
                                                                     119
      <210> 227
     <211> 818
      <212> DNA
     <213> Homo sapien
      <400> 227
                                                                      60
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tttttgctac atatggggtc ccttttcatt ctttgcaaaa acactgggtt ttctgagaac
                                                                     120
acggacggtt cttagcacaa tttgtgaaat ctgtgtaraa ccgggctttg caggggagat
                                                                     180
                                                                     240
aattttcctc ctctggagga aaggtggtga ttgacaggca gggagacagt gacaaggcta
                                                                     300
gagaaagcca cgctcggcct tctctgaacc aggatggaac ggcagacccc tgaaaacgaa
gettgteece ttecaateag ecaettetga gaaceecat etaactteet aetggaaaag
                                                                     360
                                                                     420
agggcctcct caggagcagt ccaagagttt tcaaagataa cgtgacaact accatctaga
ggaaagggtg cacceteage agagaageeg agagettaac tetggtegtt tecagagaca
                                                                     480
                                                                     540
acctgctggc tgtcttggga tgcgcccagc ctttgagagg ccactacccc atgaacttct
                                                                     600
gccatccact ggacatgaag ctgaggacac tgggcttcaa cactgagttg tcatgagagg
gacaggetet geceteaage eggetgaggg cagcaaceae teteeteece ttteteaege
                                                                     660
aaagccattc ccacaaatcc agaccatacc atgaagcaac gagacccaaa cagtttggct
                                                                     720
caagaggata tgaggactgt ctcagcctgg ctttgggctg acaccatgca cacacacaag
                                                                     780
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gtccacttct aggttttcag cctagatggg agtcgtgt	818
<210> 228 <211> 744 <212> DNA <213> Homo sapien	
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gtcatgacgt ttgacatacc tttggaacga gcctcctcct tggaagatgg aagaccgtgt	120 180
togtggcoga cotggcotot cotggcotgt ttottaagat goggagtoac atttcaatgg	240
taggaaaagt ggcttcgtaa aatagaagag cagtcactgt ggaactacca aatggcgaga	300
tgctcggtgc acattggggt gctttgggat aaaagattta tgagccaact attctctggc	360
accagattet aggecagttt gttecaetga agetttteee acageagtee acetetgeag getggeaget gaatggettg eeggtggete tgtggeaaga teacaetgag ategatgggt	420
gagaaggeta ggatgettgt etagtgttet tagetgteac gttggeteet tecaggttgg	480
ccagacggtg ttggccactc ccttctaaaa cacaggcgcc ctcctggtga cagtgacccg	540
ccgtggtatg ccttggccca ttccagcagt cccagttatg catttcaagt ttggggtttg	600
ttettttegt taatgtteet etgtgttgte agetgtette attteetggg etaageagea	660
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<pre>&lt;400&gt; 268 aatgtctcac tcaactactt cccagcctac cgtggcctaa ttctgggagt tttcttctta gatcttggga gagctggttc ttctaaggag aaggaggaag gacagatgta actttggatc tcgaagagga agtctaatgg aagtaattag tcaacggtcc ttgtttagac tcttggaata tgctgggtgg ctcagtgagc ccttttggag aaagcaagta ttattcttaa ggagtaacca cttcccattg ttctactttc taccatcatc aattgtatat tatgtattct ttggagaact a</pre>	60 120 180 240 300 301
<210> 269 <211> 301 <212> DNA <213> Homo sapien	

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<400> 269
taacaatata cactagctat ctttttaact gtccatcatt agcaccaatq aaqattcaat
                                                                         60
aaaattacct ttattcacac atctcaaaac aattctgcaa attcttagtg aagtttaact
                                                                       120
atagtcacag accttaaata ttcacattgt tttctatgtc tactgaaaat aagttcacta
                                                                       180
cttttctgga tattctttac aaaatcttat taaaattcct ggtattatca cccccaatta
                                                                       240
tacagtagca caaccacctt atgtagtttt tacatgatag ctctgtagaa gtttcacatc
                                                                       300
                                                                       301
      <210> 270
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 270
cattgaagag cttttgcgaa acatcagaac acaagtgctt ataaaattaa ttaagcctta
                                                                        60
cacaagaata catattcctt ttatttctaa ggagttaaac atagatgtag ctgatgtgga
                                                                       120
gagettgetg gtgeagtgea tattggataa caetatteat ggeegaattg atcaagteaa
                                                                       180
ccaactcctt gaactggatc atcagaagaa gggtggtgca cgatatactg cactagataa
                                                                       240
tggaccaacc aactaaattc tctcaccagg ctgtatcagt aaactggctt aacaqaaaac
                                                                       300
                                                                       301
      <210> 271
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(301)
      <223> n = A, T, C or G
      <400> 271
aaaaggttct cataagatta acaatttaaa taaatatttg atagaacatt ctttctcatt
                                                                        60
tttatagete atetttaggg ttgatattea gtteatgett ceettgetgt tettgateea
                                                                       120
gaattgcaat cacttcatca gcctgtattc gctccaattc tctataaagt gggtccaaqq
                                                                       180
tgaaccacag agccacagca cacctctttc ccttggtgac tgccttcacc ccatganggt
                                                                       240
tetetectee agatganaac tgateatgeg cecacatttt gggttttata gaagcaqtea
                                                                       300
                                                                       301
      <210> 272
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 272
taaattgcta agccacagat aacaccaatc aaatggaaca aatcactgtc ttcaaatgtc
                                                                        60
ttatcagaaa accaaatgag cctggaatct tcataatacc taaacatgcc gtatttagga
                                                                       120
tecaataatt eeeteatgat gageaagaaa aattetttge geaceeetee tqeatecaca
                                                                       180
gcatcttctc caacaaatat aaccttgagt ggcttcttgt aatctatgtt ctttgttttc
                                                                       240
ctaaggactt ccattgcatc tcctacaata ttttctctac gcaccactag aattaagcag
                                                                       300
g
                                                                       301
```

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<210> 273
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (301)
      \langle 223 \rangle n = A,T,C or G
      <400> 273
                                                                         60
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aqaqanqctq qqacatggat aatcacwtaa tttgctayta tyactttaat ctgactygaa
                                                                        120
gaaccgtcta aaaataaaat ttaccatgtc dtatattcct tatagtatgc ttatttcacc
                                                                        180
ttytttctqt ccaqaqaqaq tatcagtqac ananatttma gggtgaamac atgmattggt
                                                                        240
gggacttnty tttacngagm accetgeeeg sgegeeeteg makengantt eegesanane
                                                                        300
                                                                        301
      <210> 274
      <211> 301
      <212> DNA
      <213> Homo sapien
     <220>
      <221> misc feature
      <222> (1)...(301)
      <223> n = A,T,C or G
      <400> 274
                                                                         60
cttatatact ctttctcaga ggcaaaagag gagatgggta atgtagacaa ttctttgagg
aacaqtaaat qattattaga gagaangaat ggaccaagga gacagaaatt aacttgtaaa
                                                                        120
tgattetett tggaatetga atgagateaa gaggeeaget ttagettgtg gaaaagteea
                                                                        180
tctaggtatg gttgcattct cgtcttcttt tctgcagtag ataatgaggt aaccgaaggc
                                                                        240
aattgtgctt cttttgataa gaagctttct tggtcatatc aggaaattcc aganaaagtc
                                                                        300
                                                                        301
      <210> 275
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(301)
      <223> n = A, T, C or G
      <400> 275
teggtgteag cagcaegtgg cattgaacat tgcaatgtgg agcccaaacc acagaaaatg
                                                                         60
gggtgaaatt ggccaacttt ctattaactt atgttggcaa ttttgccacc aacagtaagc
                                                                        120
tggcccttct aataaaagaa aattgaaagg tttctcacta aacggaatta agtagtggag
                                                                        180
```

```
tcaagagact cocaggcete agegtacetg ceegggegge egetegaage egaattetge
                                                                        240
agatatecat caeactggeg gnegetegan catgeateta gaaggneeaa ttegeeetat
                                                                        300
                                                                        301
      <210> 276
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 276
tgtacacata ctcaataaat aaatgactgc attgtggtat tattactata ctgattatat
                                                                         60
ttatcatgtg acttctaatt agaaaatgta tccaaaagca aaacagcaga tatacaaaat
                                                                        120
taaagagaca gaagatagac attaacagat aaggcaactt atacattgag aatccaaatc
                                                                        180
caatacattt aaacatttgg gaaatgaggg ggacaaatgg aagccagatc aaatttgtgt
                                                                        240
aaaactattc agtatgtttc ccttgcttca tgtctgagaa ggctctcctt caatggggat
                                                                        300
                                                                        301
      <210> 277
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(301)
      <223> n = A, T, C \text{ or } G
      <400> 277
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                                                                         60
atacagagga cttggaggaa gcagagcaac tgaatttaat ttaaaagaag gaaaacattg
                                                                        120
gaatcatggc actcctgata ctttcccaaa tcaacactct caatgcccca ccctcgtcct
                                                                        180
caccatagtg gggagactaa agtggccacg gatttgcctt angtgtgcag tgcgttctga
                                                                        240
                                                                        300
gttcnctgtc gattacatct gaccagtctc ctttttccga agtccntccg ttcaatcttg
                                                                        301
      <210> 278
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(301)
      <223> n = A, T, C or G
      <400> 278
taccactaca ctccagcctg ggcaacagag caagacctgt ctcaaagcat aaaatggaat
                                                                         60
aacatatcaa atgaaacagg gaaaatgaag ctgacaattt atggaagcca gggcttgtca
                                                                        120
cagtetetae tgttattatg cattacetgg gaatttatat aagecettaa taataatgee
                                                                        180
aatgaacatc tcatgtgtgc tcacaatgtt ctggcactat tataagtgct tcacaggttt
                                                                        240
tatgtgttct tcgtaacttt atggantagg tactcggccg cgaacacgct aagccgaatt
                                                                        300
```

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С
                                                                        301
      <210> 279
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(301)
      <223> n = A,T,C \text{ or } G
      <400> 279
aaagcaggaa tgacaaagct tgcttttctg gtatgttcta ggtgtattgt gacttttact
                                                                         60
gttatattaa ttgccaatat aagtaaatat agattatata tgtatagtgt ttcacaaaqc
                                                                        120
ttagacettt acettecage caceccacag tgettgatat tteagagtea gteattggtt
                                                                        180
atacatgtgt agttccaaag cacataagct agaanaanaa atatttctag ggagcactac
                                                                        240
catctgtttt cacatgaaat gccacacaca tagaactcca acatcaattt cattgcacag
                                                                        300
                                                                        301
      <210> 280
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 280
ggtactggag ttttcctccc ctgtgaaaac gtaactactg ttgggagtga attgaggatg
                                                                         60
tagaaaggtg gtggaaccaa attgtggtca atggaaatag gagaatatgg ttctcactct
                                                                        120
tgagaaaaaa acctaagatt agcccaggta gttgcctgta acttcagttt ttctgcctgg
                                                                        180
gtttgatata gtttagggtt ggggttagat taagatctaa attacatcag gacaaagaga
                                                                        240
cagactatta actccacagt taattaagga ggtatgttcc atgtttattt gttaaagcag
                                                                        300
                                                                        301
      <210> 281
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 281
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                                                                         60
gccgagcaat ccaaatcctg aatgaagggg catcttctga aaaaggagat ctgaatctca
                                                                        120
atgtggtagc aatggcttta tcgggttata cggatgagaa gaactccctt tggagagaaa
                                                                        180
tgtgtagcac actgcgatta cagctaaata acccgtattt gtgtgtcatg tttqcatttc
                                                                        240
tgacaagtga aacaggatet tacgatggag ttttgtatga aaacaaaqtt qeaqtacete
                                                                        300
                                                                        301
      <210> 282
      <211> 301
      <212> DNA
      <213> Homo sapien
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<400> 282
caggtactac agaattaaaa tactgacaag caagtagttt cttggcgtgc acgaattgca
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tccagaaccc aaaaattaag aaattcaaaa agacattttg tgggcacctg ctagcacaqa
                                                                        120
agegeagaag caaageecag geagaaceat getaacetta cageteagee tgeacagaag
                                                                        180
cgcagaagca aagcccaggc agaaccatgc taaccttaca gctcagcctg cacaqaaqcq
                                                                        240
cagaagcaaa gcccaggcag aacatgctaa ccttacagct cagcctgcac aqaagcacag
                                                                        300
                                                                        301
      <210> 283
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 283
atctgtatac ggcagacaaa ctttatarag tgtagagagg tgagcgaaag gatgcaaaag
                                                                         60
cactttgagg gctttataat aatatgctgc ttgaaaaaaa aaatgtgtag ttgatactca
                                                                        120
gtgcatctcc agacatagta aggggttgct ctgaccaatc aggtgatcat tttttctatc
                                                                        180
acttcccagg ttttatgcaa aaattttgtt aaattctata atggtgatat qcatctttta
                                                                        240
ggaaacatat acatttttaa aaatctattt tatgtaagaa ctgacagacg aatttgcttt
                                                                        300
                                                                        301
      <210> 284
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 284
caggtacaaa acgctattaa gtggcttaga atttgaacat ttgtggtctt tatttacttt
                                                                        60
gcttcgtgtg tgggcaaagc aacatcttcc ctaaatatat attaccaaqa aaaqcaaqaa
                                                                        120
gcagattagg tttttgacaa aacaaacagg ccaaaagggg gctgacctgg agcagagcat
                                                                        180
ggtgagaggc aaggcatgag agggcaagtt tgttgtggac agatctgtgc ctactttatt
                                                                        240
actggagtaa aagaaaacaa agttcattga tgtcgaagga tatatacagt gttagaaatt
                                                                       300
                                                                       301
      <210> 285
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(301)
      <223> n = A, T, C \text{ or } G
      <400> 285
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                                                                        60
aatgatcatt agtgttttaa aaaaaatact gaaaactcct tctgcatccc aatctctaac
                                                                       120
caggaaagca aatgctattt acagacctgc aagccctccc tcaaacnaaa ctatttctgg
                                                                       180
attaaatatg tetgaettet tttgaggtea caegaetagg caaatgetat ttaegatetg
                                                                       240
caaaagctgt ttgaagagtc aaagccccca tgtgaacacg atttctggac cctgtaacag
                                                                       300
                                                                       301
```

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<210> 286
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 286
taccactgca ttccagcctg ggtgacagag tgagactccg tctccaaaaa aaactttgct
                                                                        60
tgtatattat ttttgcctta cagtggatca ttctagtagg aaaggacagt aagattttt
                                                                       120
atcaaaatgt gtcatgccag taagagatgt tatattcttt tctcatttct tccccaccca
                                                                       180
aaaataagct accatatagc ttataagtct caaatttttg ccttttacta aaatqtqatt
                                                                       240
gtttctgttc attgtgtatg cttcatcacc tatattaggc aaattccatt ttttcccttg
                                                                       300
                                                                       301
      <210> 287
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 287
tacagatctg ggaactaaat attaaaaatg agtgtggctg gatatatgga gaatgttggg
                                                                        60
cccagaagga acgtagagat cagatattac aacagctttg ttttgagggt tagaaatatg
                                                                       120
aaatgatttg gttatgaacg cacagtttag gcagcagggc cagaatcctg accetetgce
                                                                       180
ccgtggttat ctcctcccca gcttggctgc ctcatgttat cacagtattc cattttgttt
                                                                       240
gttgcatgtc ttgtgaagcc atcaagattt tctcgtctgt tttcctctca ttggtaatgc
                                                                       300
                                                                       301
      <210> 288
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 288
gtacacctaa ctgcaaggac agctgaggaa tgtaatgggc agccgctttt aaagaagtag
                                                                        60
agtcaatagg aagacaaatt ccagttccag ctcagtctgg gtatctgcaa aqctqcaaaa
                                                                       120
gatctttaaa gacaatttca agagaatatt tccttaaagt tggcaatttg gagatcatac
                                                                       180
aaaagcatct gcttttgtga tttaatttag ctcatctggc cactggaaga atccaaacag
                                                                       240
tetgeettaa tittggatga atgeatgatg gaaatteaat aatttagaaa gttaaaaaaa
                                                                       300
                                                                       301
      <210> 289
      <211> 301
      <212> DNA
      <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1)...(301)
     <223> n = A,T,C or G
     <400> 289
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60
ggtacactgt ttccatgtta tgtttctaca cattgctacc tcagtgctcc tggaaactta
                                                                        120
gettttgatg tetecaagta gtecacette atttaactet ttgaaactgt atcatetttg
ccaagtaaga gtggtggcct atttcagctg ctttgacaaa atgactggct cctgacttaa
                                                                        180
cgttctataa atgaatgtgc tgaagcaaag tgcccatggt ggcggcgaan aagagaaaga
                                                                        240
tgtgttttgt tttggactet ctgtggtece ttecaatget gtgggtttee aaccagngga
                                                                        300
                                                                        301
      <210> 290
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(301)
      <223> n = A, T, C or G
      <400> 290
acactqaqct cttcttgata aatatacaga atgcttggca tatacaagat tctatactac
                                                                         60
tqactqatct gttcatttct ctcacagctc ttacccccaa aagcttttcc accctaagtg
                                                                        120
ttctgacctc cttttctaat cacagtaggg atagaggcag anccacctac aatgaacatg
                                                                        180
gagttctatc aagaggcaga aacagcacag aatcccagtt ttaccattcg ctagcagtgc
                                                                        240
tgccttgaac aaaaacattt ctccatgtct cattttcttc atgcctcaag taacagtgag
                                                                        300
                                                                        301
a
      <210> 291
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 291
caggtaccaa tttcttctat cctagaaaca tttcatttta tgttgttgaa acataacaac
                                                                         60
tatatcagct agattttttt tctatgcttt acctgctatg gaaaatttga cacattctgc
                                                                        120
tttactcttt tgtttatagg tgaatcacaa aatgtatttt tatgtattct gtagttcaat
                                                                        180
agccatggct gtttacttca tttaatttat ttagcataaa gacattatga aaaggcctaa
                                                                        240
acatgagett caetteecca etaactaatt ageatetgtt atttettaac egtaatgeet
                                                                        300
                                                                        301
      <210> 292
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(301)
      <223> n = A, T, C \text{ or } G
      <400> 292
accttttagt agtaatgtct aataataaat aagaaatcaa ttttataagg tccatatagc
                                                                         60
tgtattaaat aatttttaag tttaaaagat aaaataccat cattttaaat gttggtattc
                                                                        120
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<210> 296 <211> 301

aaaaccaaag natataaccg aaaggaaaaa cagatgagac ataaaatgat ttgcnagatg ggaaatatag tasttyatga atgttnatta aattccagtt ataatagtgg ctacacactc tcactacaca cacagacccc acagtcctat atgccacaaa cacatttcca taacttgaaa a	180 240 300 301
<210> 293 <211> 301 <212> DNA <213> Homo sapien	
<pre>&lt;400&gt; 293 ggtaccaagt gctggtgcca gcctgttacc tgttctcact gaaaagtctg gctaatgctc ttgtgtagtc acttctgatt ctgacaatca atcaatcaat ggcctagagc actgactgtt aacacaaacg tcactagcaa agtagcaaca gctttaagtc taaatacaaa gctgttctgt gtgagaattt tttaaaaggc tacttgtata ataacccttg tcatttttaa tgtacctcgg ccgcgaccac gctaagccga attctgcaga tatccatcac actggcggcc gctcgagcat g</pre>	60 120 180 240 300 301
<210> 294 <211> 301 <212> DNA <213> Homo sapien	
<220> <221> misc_feature <222> (1)(301) <223> n = A,T,C or G	
<pre>&lt;400&gt; 294 tgacccataa caatatacac tagctatctt tttaactgtc catcattagc accaatgaag attcaataaa attaccttta ttcacacatc tcaaaacaat tctgcaaatt cttagtgaag tttaactata gtcacaganc ttaaatattc acattgttt ctatgtctac tgaaaataag ttcactactt ttctgggata ttctttacaa aatcttatta aaattcctgg tattatcacc cccaattata cagtagcaca accaccttat gtagtttta catgatagct ctgtagaggt t</pre>	60 120 180 240 300 301
<210> 295 <211> 305 <212> DNA <213> Homo sapien	
<pre>&lt;400&gt; 295 gtactctttc tctcccctcc tctgaattta attctttcaa cttgcaattt gcaaggatta cacatttcac tgtgatgtat attgtgttgc aaaaaaaaaa</pre>	60 120 180 240 300 305

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<212> DNA
      <213> Homo sapien
      <400> 296
                                                                         60
aggtactatg ggaagctgct aaaataatat ttgatagtaa aagtatgtaa tgtgctatct
                                                                        120
cacctagtag taaactaaaa ataaactgaa actttatgga atctgaagtt attttccttg
attaaataga attaataaac caatatgagg aaacatgaaa ccatgcaatc tactatcaac
                                                                        180
                                                                        240
tttgaaaaag tgattgaacg aaccacttag ctttcagatg atgaacactg ataagtcatt
tqtcattact ataaatttta aaatctgtta ataagatggc ctatagggag gaaaaagggg
                                                                        300
                                                                        301
      <210> 297
      <211> 300
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(300)
      \langle 223 \rangle n = A,T,C or G
      <400> 297
actgagtttt aactggacgc caagcaggca aggctggaag gttttgctct ctttgtgcta
                                                                         60
                                                                        120
aaqqttttqa aaaccttgaa ggagaatcat tttgacaaga agtacttaag agtctagaga
                                                                        180
acaaagangt gaaccagetg aaageteteg ggggaanett acatgtgttg ttaggeetgt
                                                                        240
tocatcattg ggagtgcact ggccatccct caaaatttgt ctgggctggc ctgagtggtc
accgcacete ggeegegace aegetaagee gaattetgea gatatecate acaetggegg
                                                                        300
      <210> 298
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(301)
      <223> n = A, T, C \text{ or } G
      <400> 298
tatggggttt gtcacccaaa agctgatgct gagaaaggcc tccctggggc ccctcccgcg
                                                                         60
qqcatctqaq aqacctqqtq ttccaqtgtt tctggaaatg ggtcccagtg ccgccggctg
                                                                         120
tgaagctctc agatcaatca cgggaagggc ctggcggtgg tggccacctg gaaccaccct
                                                                         180
                                                                         240
gtcctgtctg tttacatttc actaycaggt tttctctggg cattacnatt tgttccccta
caacagtgac ctgtgcattc tgctgtggcc tgctgtgtct gcaggtggct ctcagcgagg
                                                                         300
                                                                         301
      <210> 299
      <211> 301
      <212> DNA
      <213> Homo sapien
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<pre>&lt;400&gt; 299 gttttgagac ggagtttcac tcttgttgcc cagactggac tgcaatggca gggtctctgc tcactgcacc ctctgcctcc caggttcgag caattctcct gcctcagcct cccaggtagc tgggattgca ggctcacgcc accataccca gctaattttt ttgtattttt agtagagacg gagtttcgcc atgttggcca gctggtctca aactcctgac ctcaagcgac ctgcctgcct cggcctccca aagtgctgga attataggca tgagtcaaca cgcccagcct aaagatattt t</pre>	60 120 180 240 300 301
<210> 300 <211> 301 <212> DNA <213> Homo sapien	
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<210> 303 <211> 301 <212> DNA <213> Homo sapien	

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tggctaatgg aactaccgct tgcatgttaa aaatggtggt ttgtgaaatg atcataggcc
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agtaacgggt atgtttttct aactgatctt ttgctcgttc caaagggacc tcaagacttc
                                                                        240
categatttt atatetgggg tetagaaaag gagttaatet gtttteeete ataaatteae
                                                                        300
                                                                        301
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      <211> 301
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                                                                        120
ctttttagtg tatcatatca ggaatcatct cacattggtt tqtqccatta ctqqtqcaqt
                                                                        180
gactttcagc cacttgggta aggtggagtt ggccatatgt ctccactgca aaattactga
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      <211> 301
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taaaggagga gaaacagata caaaatctcc aactcaqtat taaqqtattc tcatqcctaq
                                                                        180
aatattggta gaaacaagaa tacattcata tggcaaataa ctaaccatgg tggaacaaaa
                                                                        240
ttctgggatt taagttggat accaangaaa ttgtattaaa agagctgttc atggaataag
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                                                                        301
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      <211> 8
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<212> DNA

<213> Homo sapien <400> 307 acagggratg aagggaaagg gagaggatga ggaagccccc ctggggattt ggtttggtcc 60 ttgtgatcag gtggtctatg gggcttatcc ctacaaagaa gaatccagaa ataggggcac 120 attgaggaat gatacttgag cccaaagagc attcaatcat tgttttattt gccttmtttt 180 cacaccattg gtgagggagg gattaccacc ctggggttat gaagatggtt gaacacccca 240 cacatagcac cggagatatg agatcaacag tttcttagcc atagagattc acagcccaga 300 gcaggaggac gcttgcacac catgcaggat gacatggggg atgcgctcgg gattggtgtg 360 aagaagcaag gactgttaga ggcaggcttt atagtaacaa gacggtgggg caaactctga 420 tttccgtggg ggaatgtcat ggtcttgctt tactaagttt tgagactggc aggtagtgaa 480 actcattagg ctgagaacct tgtggaatgc acttgaccca sctgatagag gaagtagcca 540 ggtgggagcc tttcccagtg ggtgtgggac atatctggca agattttgtg gcactcctgg 600 ttacagatac tggggcagca aataaaactg aatcttg 637 <210> 308 <211> 647 <212> DNA <213> Homo sapien <220> <221> misc\_feature <222> (1)...(647) <223> n = A, T, C or G<400> 308 acgattttca ttatcatgta aatcgggtca ctcaaggggc caaccacagc tgggagccac 60 tgctcagggg aaggttcata tgggactttc tactgcccaa ggttctatac aggatataaa 120 ggngcctcac agtatagatc tggtagcaaa gaagaagaaa caaacactga tctctttctg 180 ccacccctct gaccctttgg aactcctctg accctttaga acaagcctac ctaatatctg 240 ctagagaaaa gaccaacaac ggcctcaaag gatctcttac catgaaggtc tcagctaatt 300 cttggctaag atgtgggttc cacattaggt tctgaatatg gggggaaggg tcaatttgct 360 cattttgtgt gtggataaag tcaggatgcc caggggccag agcagggggc tgcttgcttt 420 gggaacaatg gctgagcata taaccatagg ttatggggaa caaaacaaca tcaaagtcac 480 tgtatcaatt gccatgaaga cttgagggac ctgaatctac cgattcatct taaggcagca 540 ggaccagttt gagtggcaac aatgcagcag cagaatcaat ggaaacaaca gaatgattgc 600 aatgteettt ttttteteet gettetgaet tgataaaagg ggaeegt 647 <210> 309 <211> 460 <212> DNA <213> Homo sapien <400> 309 actttatagt ttaggctgga cattggaaaa aaaaaaaagc cagaacaaca tgtgatagat 60 aatatgattg gctgcacact tccagactga tgaatgatga acgtgatgga ctattgtatg 120 gagcacatct tcagcaagag ggggaaatac tcatcatttt tggccagcag ttgtttgatc 180 accaaacatc atgccagaat actcagcaaa ccttcttagc tcttgagaag tcaaagtccg 240 ggggaattta ttcctggcaa ttttaattgg actccttatg tgagagcagc ggctacccag 300 ctggggtggt ggagcgaacc cgtcactagt ggacatgcag tggcagagct cctggtaacc 360

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acctagagga atacacaggc acatgtgtga tgccaagcgt gacacctgta gcactcaaat
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taggaaagag aaacacagaa ggaagagaca caataaaagt cattatgtat tctgtgagaa
                                                                       180
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gtcagacagt aagatttgtg ggaaatgggt tggtttgttg tatggtatgt attttagcaa
taatetttat ggeagagaaa getaaaatee tttagettge gtgaatgate aettgetgaa
                                                                       300
ttcctcaagg taggcatgat gaaggagggt ttagaggaga cacagacaca atgaactgac
                                                                       360
ctagatagaa agccttagta tactcagcta ggaatagtga ttctgagggc acactgtgac
                                                                       420
                                                                       480
atgattatgt cattacatgt atggtagtga tggggatgat aggaaggaag aacttatggc
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     <221> misc feature
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catttacagc atttaaaatg tgttcagcat gaaatattag ctacagggga agctaaataa
                                                                       180
attaaacatg gaataaagat ttgtccttaa atataatcta caagaagact ttgatatttg
                                                                       240
tttttcacaa gtgaagcatt cttataaagt gtcataacct ttttggggaa actatgggaa
                                                                       300
aaaatgggga aactctgaag ggttttaagt atcttacctg aagctacaga ctccataacc
                                                                       360
tetetttaea gggageteet geageeeeta cagaaatgag tggetgagat tettgattge
                                                                       420
acagcaagag cttctcatct aaaccettte cetttttagt atctgtgtat caagtataaa
                                                                       480
agttctataa actgtagtnt acttatttta atccccaaag cacagt
                                                                       526
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                                                                       120
ccatttetet ttecetteea cetgecagtt ttgetgacte teaacttgte atgagtgtaa
                                                                       180
gcattaagga cattatgctt cttcgattct gaagacaggc cctgctcatg gatgactctg
                                                                       240
gcttcttagg aaaatatttt tcttccaaaa tcagtaggaa atctaaactt atcccctctt
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tgcagatgtc tagcagcttc agacatttgg ttaagaaccc atgggaaaaa aaaaaatcct
                                                                       360
tgctaatgtg gtttcctttg taaaccanga ttcttatttg nctggtatag aatatcagct
                                                                       420
ctgaacgtgt ggtaaagatt tttgtgtttg aatataggag aaatcagttt gctgaaaagt
                                                                       480
tagtcttaat tatctattgg
                                                                       500
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      <211> 718
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                                                                       120
ctgctgaaat ggagataatt aacatcacta gaaacagcaa gatgacaata taatgtctaa
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gtagtgacat gtttttgcac atttccagcc cttttaaata tccacacaca caggaagcac
                                                                       240
aaaaggaagc acagagatcc ctgggagaaa tgcccggccg ccatcttggg tcatcgatga
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gcctcgccct gtgcctgntc ccgcttgtga gggaaggaca ttagaaaatg aattgatgtg
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agatttgaaa tgaagtcaca aagtgagcat taccaatgag aggaaaacag acgagaaaat
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cttgatggtt cacaagacat gcaacaaaca aaatggaata ctgtgatgac acgagcagcc
                                                                       540
aactggggag gagataccac ggggcagagg tcaggattct ggccctgctg cctaactgtg
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cgttatacca atcatttcta tttctaccct caaacaagct gtngaatatc tgacttacgg
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ttcttntggc ccacattttc atnatccacc ccntcntttt aannttantc caaantgt
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cataatcaaa tatagctgta gtacatgttt tcattggtgt agattaccac aaatgcaagg
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caacatgtgt agatetettg tettattett ttgtetataa tactgtattg tgtagtecaa
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gctctcggta gtccagccac tgtgaaacat gctcccttta gattaacctc gtggacgctc
                                                                       240
ttgttgtatt getgaactgt agtgeeetgt attttgette tgtetgtgaa ttetgttget
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tetggggeat tteettgtga tgeagaggae caecaeag atgaeageaa tetgaatt
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      <210> 315
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<213> Homo sapien

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<210> 316 <211> 151 <212> DNA <213> Homo sapier	n				
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<210> 319 <211> 151 <212> DNA <213> Homo sapier	n				
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<210> 320 <211> 150					

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gagtgttcta cagcttacag taaataccat
                                                                        150
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      <211> 151
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      <213> Homo sapien
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tagggtggca ttgtaaccag ctatggcata ggtgttaacc aaaggctgag taaacatggg
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tgcctctgag aaatcaaagt cttcatacac t
                                                                        151
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attgtgcagg gctcgcttca nacttccagt t
                                                                        151
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      <211> 151
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      <221> misc_feature
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nagactcant tactacccag tttgtggttt twtgggagaa atgtaactgg acagttagct
                                                                        120
gttcaatyaa aaagacactt ancccatgtg g
                                                                        151
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      <211> 461
      <212> DNA
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<213> Homo sapien
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      <221> misc_feature
      <222> (1)...(461)
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agagttacta cgaatcccat cttggttcca gctatatcac tgacagcatg gtagaagact
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gcgaacctca cttctagact ttcacggtgg gacgaaacgg gttcagaaac tgccaggggc
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ctcatacagg gatatcaaaa taccctttgt gctacccagg ccctggggaa tcaggtgact
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cacacaaatg caatagttgg tcactgcatt tttacctgaa ccaaagctaa acccggtgtt
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gccaccatgc accatggcat gccagagttc aacactgttg ctcttgaaaa ttgggtctga
                                                                        420
aaaaacgcac aagagcccct gccctgccct agctgangca c
                                                                        461
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                                                                       120
agtaagagtg gtggcctatt tcagctgctt tgacaaaatg actggctcct gacttaacgt
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                                                                       240
gttttgtttt ggactctctg tggtcccttc caatgctgtg ggtttccaac caggggaagg
                                                                       300
gtcccttttg cattgccaag tgccataacc atgagcacta cgctaccatg gttctgcctc
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cctccctcag actcagaggt ccaagccccc aacccctcct tccccagacc cagaggtcca
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      <211> 220
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Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val
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Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly
                           40
Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu
Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu Ala
Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp
                                   90
Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn
           100
                               105
Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met Pro
                           120
                                              125
Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu Val Cys
                       135
Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala Gly
                   150
                                      155
Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly Pro
               165
                                  170
Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys Ala
                               185
Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu Cys Lys
                           200
Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
   210
                       215
                                          220
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<400> 328

<213> Homo sapien

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900

960

1020

1080

1140

1200

1215

atccgcagtg ggtgctgtca gccacacact gtttccagaa ctcctacacc atcgggctgg gcctgcacag tcttgaggcc gaccaagagc cagggagcca gatggtggag gcca	180 234
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Pro His Ser Gln Pro Trp Gln Ala Ala Leu Val Met Glu Asn Glu Leu 20 25 30	
Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val Leu Ser Ala Thr 35 40 45	
His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly Leu His Ser Leu 50 55 60	
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<sup>&</sup>lt;210> 334

<sup>&</sup>lt;211> 2417

<sup>&</sup>lt;212> DNA

<sup>&</sup>lt;213> Homo sapien

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<sup>&</sup>lt;210> 336

<sup>&</sup>lt;211> 147

<sup>&</sup>lt;212> PRT

## <213> Homo sapien

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<210> 340

<211> 483

<212> DNA

<213> Homo sapien

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                                                                    1860
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<400> 376

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 Val
 Asp
 Ser
 Phe

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 Ala
 Gly
 Ser
 Asp
 Leu
 Leu
 Ser
 Arg
 Ser
 Leu
 Met
 Ala
 Glu
 Glu
 Arg
 Arg
 Ile
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Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr Ala Leu Thr Lys Ala
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Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr
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Ala Val Tyr Asn Glu Asp Lys Leu Met Ala Lys Ala Leu Leu Tyr
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Leu Gly Ile His Glu Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys
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Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu
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Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile Val Ser Pro Leu Leu
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Ala Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile Val Ser Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His Val Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile Ser Ser Glu Asn Ser Asn Pro Glu Asn Val Ser Arg Thr Arg Asn Lys Pro Arg Thr His Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser Ser Val Lys Lys Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys Cys Arg Cys Phe Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arq Gly Ser Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu Asp Lys Leu His Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val Val Lys Leu Leu Asp Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys Ala Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu Gly Val His Glu Gln Lys

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Leu Asp Ar	g Tyr Gly	Arg Thr 695		u Ile Lei	1 Ala V 700	al Cys	Cys G	ly
Ser Ala Se 705	r Ile Val	Ser Leu 710	Leu Le	u Glu Glr 719		le Asp		er 20
Ser Gln As	Leu Ser 725		Thr Al	a Arg Glı 730	ı Tyr A	la Val	Ser S 735	er
His His Hi	Val Ile 740	Cys Gln	Leu Le 74		Tyr L	ys Glu 750	Lys G	ln
Met Leu Ly 75	5		760		7	65		-
Leu Thr Se 770		775			780			
Gln Pro Gl	_	790		795	5	_	8	00
Arg Glu Va	805			810			815	
Leu Leu Gl	820		82	5	_	830	-	
Gly Leu Il 83	5		840		8-	45		
Pro Asp As 850		855	_	_	860			
Asp Tyr Ly 865	_	870	_	875	5		8	80
Pro Glu Gl	885			890			895	
Glu Gly Se	900	_	90	5		910		
Glu Glu Me	5	_	920		9:	25		
Leu Thr As		935			940			
Pro Arg Ly 945	_	950		955	5	_	9	60
Asn Glu Gl	965			970			975	
Cys Glu Gl	980	_	98	5		990		
Glu Glu Ly 99	5		1000	-	1	005		
Leu Ser Cy 1010		101	5		1020			
Arg Glu Gl	ı Ile Ala	Met Leu 1030	Arg Le		_	hr Met	_	
1025 Gln Ser Gln Leu Pro			His Me	1035 Met Val Val Glu Va				.04 let.
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Pro Ala Al	s Ser Ser 1060	vaı Lys	Lys Pr 10		леи A:	rg Ser 1070	_	iet

Gly Lys Trp Cys Cys Arg Cys Phe Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu Asp Lys Leu His Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val Val Lys Leu Leu Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr Ala Leu Ile Lys Ala Val Gln Cys 1250 1255 Gln Glu Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys Ala Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile Val Ser Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His His Val Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser Gln Pro Glu Lys Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Val Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly Leu Leu Glu Asn Leu Thr Asn Gly Val Thr Ala Gly

1475 1480 Asn Gly Asp Asn Gly Leu Ile Pro Gln Arg Lys Ser Arg Thr Pro Glu 1490 1495 1500 Asn Gln Gln Phe Pro Asp Asn Glu Ser Glu Glu Tyr His Arg Ile Cys 1510 1515 Glu Leu Val Ser Asp Tyr Lys Glu Lys Gln Met Pro Lys Tyr Ser Ser 1530 1525 Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu 1545 1550 1540 Ser Gln Arg Leu Glu Gly Ser Glu Asn Gly Gln Pro Glu Lys Arg Ser 1555 1560 Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Leu Glu Asn Phe 1575 1580 Met Ala Ile Glu Glu Met Lys Lys His Gly Ser Thr His Val Gly Phe 1590 1595 Pro Glu Asn Leu Thr Asn Gly Ala Thr Ala Gly Asn Gly Asp Asp Gly 1605 1610 Leu Ile Pro Pro Arg Lys Ser Arg Thr Pro Glu Ser Gln Gln Phe Pro 1620 1625 Asp Thr Glu Asn Glu Glu Tyr His Ser Asp Glu Gln Asn Asp Thr Gln 1640 1645 Lys Gln Phe Cys Glu Glu Gln Asn Thr Gly Ile Leu His Asp Glu Ile 1660 1655 Leu Ile His Glu Glu Lys Gln Ile Glu Val Val Glu Lys Met Asn Ser 1675 1670 Glu Leu Ser Leu Ser Cys Lys Lys Glu Lys Asp Ile Leu His Glu Asn 1690 1685 Ser Thr Leu Arg Glu Glu Ile Ala Met Leu Arg Leu Glu Leu Asp Thr 1700 1705 Met Lys His Gln Ser Gln Leu 1715 <210> 379 <211> 656 <212> PRT <213> Homo sapien <400> 379 Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser Ser Val Lys Lys 5 10 Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys Cys Arg Cys Phe 25 Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp 40 His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp 55 60 Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val 70 75

Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn

Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser

			100					105					110		
Glv	Lve	Ser		Val	Gly	Δla	Ттп		Agn	Тугт	Asn	Δen		Δla	Dhe
OT Y	шуы	115	Lly 5	val	OT y	nia	120	O ± y	risp	+ y -	TOP	125	DCI	лια	LIIC
Mat	C3.,,		7 200		цiа	77-7		C1 32	C111	Λαn	T 011		Tara	T 011	uia
Met		PIO	Arg	ıyı	His		Arg	GTÅ	GIU	Asp		Asp	пув	ьeu	HIS
70	130	77-	П	//////////////////////////////////////	~1	135	7707	Dese	7	T	140	T	<b>-1</b> -	77-7	N4 - L
_	Ата	Ата	rrp	rrp	Gly	ьуѕ	vaı	Pro	Arg	_	Asp	Leu	тте	vaı	
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Leu	Arg	Asp	Thr		Val	Asn	Lys	Lys		Lys	GIn	Lys	Arg		Ala
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Lys	Phe	Leu	Ile	Lys	Lys	Lys	Ala	Asn	Leu	Asn	Ala	Leu	Asp	Arg	Tyr
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Val	Ser	Leu	Leu	Leu	Glu	Gln	Asn	Ile	Asp	Val	Ser	Ser	Gln	Asp	Leu
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Ser	Gly	Gln	Thr	Ala	Arg	Glu	Tyr	Ala	Val	Ser	Ser	His	His	His	Val
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Ile	Cys	Gln	Leu	Leu	Ser	Asp	Tyr	Lys	Glu	Lys	Gln	Met	Leu	Lys	Ile
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Ser	Ser	Glu	Asn	Ser	Asn	Pro	Glu	Gln	Asp	Leu	Lys	Leu	Thr	Ser	Glu
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Glu	Glu	Ser	Gln	Arg	Phe	Lys	Gly	Ser	Glu	Asn	Ser	Gln	Pro	Glu	Lys
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Met	Ser	Gln	Glu	Pro	Glu	Ile	Asn	Lys	Asp	Gly	Asp	Arq	Glu	Val	Glu
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Glu	Glu	Met	Lys	Lys	His	Glu	Ser	Asn		Val	Gly	Leu	Leu		Asn
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Leu	Thr	Asn		Val	Thr	Ala	Glv	Asn	Glv	Asp	Asn	Glv		Ile	Pro
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Gln	Ara		Ser	Ara	Thr	Pro		Asn	Gln	Gln	Phe		Asn	Asn	Glu
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Ser		Glu	Tvr	His	Arg		Cvs	Glu	Len	Val		Asn	Tvr	Lvs	Glu
465			-1-		470		J, 5		_~~	475			-1-	-10	480
	GIn	Met	Pro	Tave	Tyr	Ser	Ser	Glu	Δgn		Agn	Pro	Glu	Gln	
~, 5				485	- y -	~	~~-	u	490	~~	11011	110	u	495	1.15P
T.eu	Tave	T.e.i	Thr		Glu	Glu	Glu	Ser		Δrα	T.e.i	Glu	<u> </u>		GJ 11
LCU	-79	LCU	500	UU1	U_U	JIU	JIU	505	U111	n.y	u	JLU	510	n G T	uru
			500					202					210		

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<213> Homo sapien

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Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His Val Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser Gln Pro Glu Lys Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Val Glu Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly Leu Leu Glu Asn Leu Thr Asn Gly Val Thr Ala Gly Asn Gly Asp Asn Gly Leu Ile Pro Gln Arg Lys Ser Arg Thr Pro Glu Asn Gln Gln Phe Pro Asp Asn Glu Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser Asp Tyr Lys Glu Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Glu Gly Ser Glu Asn Gly Gln Pro Glu Lys Arg Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Leu Glu Asn Phe Met Ala Ile Glu Glu Met Lys Lys His Gly Ser Thr His Val Gly Phe Pro Glu Asn Leu Thr Asn Gly Ala Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro Pro Arg Lys Ser Arg Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu Asn Glu Glu Tyr His Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe Cys Glu Glu Gln Asn Thr Gly Ile Leu His Asp Glu Ile Leu Ile His Glu Glu Lys Gln Ile

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<212> DNA
<213> Homo sapiens
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cqtcagattt gatgatttcc tagcaggact tacagaaata aagagctatc atgctgtggt 1920
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cccagctgat agaggaagta gccaggtggg agcctttccc agtgggtgtg ggacatatct 3180
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<211> 155
<212> PRT
<213> Homo sapiens
<400> 383
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                                     10
Gly Lys Arg Gly Pro Leu Leu Gln Gly Leu Thr Trp Ala Thr Gly Gly
             20
His Cys Phe Ser Ser Glu Glu Ser Gly Ala Val Asp Gly Ala Gly Gln
Lys Lys Asp Arg Ala Trp Leu Arg Cys Pro Glu Ala Val Ala Gly Phe
     50
                         55
                                             60
Pro Leu Gly Ser Asp Cys Arg Glu Gly Gly Arg Gln Gly Cys Gly Gly
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70

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Ser Asp Asp Glu Asp Asp Leu Gly Val Ala Pro Gly Leu Ala Pro Ala
Trp Ala Leu Thr Gln Pro Pro Ser Gln Ser Pro Gly Pro Gln Ser Leu
                                105
                                                     110
            100
Pro Ser Thr Pro Ser Ser Ile Trp Pro Gln Trp Val Ile Leu Ile Thr
                            120
        115
                                                 125
Glu Leu Thr Ile Pro Ser Pro Ala His Gly Pro Pro Trp Leu Pro Asn
                        135
                                            140
Ala Leu Glu Arg Gly His Leu Val Arg Glu
145
                    150
<210> 384
<211> 557
<212> DNA
<213> Homo sapiens
<400> 384
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ggggaagggt cccttttgca ttgccaagtg ccataaccat gagcactact ctaccatggt 180
tctqcctcct qqccaagcaq qctqqtttqc aagaatgaaa tgaatgattc tacagctagg 240
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ccttcttatt tatqtqaaca actqtttqtc tttttttqta tctttttaa actqtaaaqt 480
tcaattgtga aaatgaatat catgcaaata aattatgcga tttttttttc aaagtaaaaa 540
                                                                   557
aaaaaaaaa aaaaaaa
<210> 385
<211> 337
<212> DNA
<213> Homo sapiens
<400> 385
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totcaaagoo atotgotgto ttogagtaog gacacatoat cactootgca ttgttgatca 180
aaacgtggag gtgcttttcc tcagctaaga agcccttagc aaaagctcga atagacttag 240
tatcagacag gtccagtttc cgcaccaaca cctgctggtt ccctgtcgtg gtctggatct 300
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<210> 386
<211> 300
<212> DNA
<213> Homo sapiens
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gcgaccttgg cccgaagget ctagcaagga cccaccgacc ccagccgcgg cggcggcggc 180
geggaetttg eeeggtgtgt ggggeggage ggaetgegtg teegeggaeg ggeagegaag 240
atgttageet tegetgeeag gaeegtggae egateeeagg getgtggtgt aaceteagee 300
<210> 387
<211> 537
<212> DNA
<213> Homo sapiens
<400> 387
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cccctcctg tgccatcatg atcagcacct atgagttcgg caaaagcttc ttccagaggc 120
tgaaccagga ceggettetg ggeggetgaa aggggeaagg aggeaaggae ceegtetete 180
ccacggatgg ggagagggca ggaggagacc cagccaagtg ccttttcctc agcactgagg 240
gagggggctt gtttcccttc cctcccggcg acaagctcca gggcagggct gtccctctgg 300
geggeeeage aetteeteag acacaaette tteetgetge teeagtegtg gggateatea 360
cttacccacc ccccaagttc aagaccaaat cttccagctg cccccttcgt gtttccctgt 420
gtttgctgta gctgggcatg tctccaggaa ccaagaagcc ctcagcctgg tgtagtctcc 480
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<210> 388
<211> 520
<212> DNA
<213> Homo sapiens
<400> 388
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tgaggttaaa ccagtttgca ttcccctaat gtggaaaaag taagaggact actcagcact 120
gtttgaagat tgcctcttct acagcttctg agaattgtgt tatttcactt gccaagtgaa 180
ggaccccctc cccaacatgc cccagcccac ccctaagcat ggtcccttgt caccaggcaa 240
ccaggaaact gctacttgtg gacctcacca gagaccagga gggtttggtt agctcacagg 300
acttccccca ccccagaaga ttagcatccc atactagact catactcaac tcaactaggc 360
tcatactcaa ttgatggtta ttagacaatt ccatttcttt ctggttatta taaacagaaa 420
atctttcctc ttctcattac cagtaaaggc tcttggtatc tttctgttgg aatgatttct 480
atgaacttgt cttattttaa tggtgggttt tttttctggt
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<210> 389
<211> 365
<212> DNA
<213> Homo sapiens
<400> 389
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gagttaaggc tggatttcag atctgcctgg ttccagccgc agtgtgccct ctgctccccc 120
aacgactttc caaataatct caccagegec ttccagetca ggegtectag aagegtettg 180
aagcetatgg ccagetgtet ttgtgtteee teteaceege etgteeteae agetgagaet 240
cccaggaaac cttcagacta ccttcctctg ccttcagcaa ggggcgttgc ccacattctc 300
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<210> 390
<211> 221
<212> DNA
<213> Homo sapiens
<220>
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<222> (1)...(221)
<223> n = A, T, C or G
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tacacggntt ctcatgggtg tggaacatct ctgcttgcgg tttcaggaag gcctctggct 120
gctctangag tctgancnga ntcgttgccc cantntgaca naaggaaagg cggagcttat 180
tcaaagtcta gagggagtgg aggagttaag gctggatttc a
                                                                    221
<210> 391
<211> 325
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(325)
<223> n = A,T,C or G
<400> 391
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ctctcgcgcc cagcctggag ctgctcctgg catctaccaa caatcagncg aggcgagcag 120
tagccagggc actgctgcca acagccagtc cnnataccat catgtnaccc ggtgngctct 180
naanttngat ntccanagcc ctacccatcn tagttctgct ctcccaccgg ntaccagccc 240
cactgoccag gaatcotaca gocagtacco tgtcccgacg tototaccta ccagtacgat 300
gagaceteeg getactacta tgace
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<210> 392
<211> 277
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(277)
\langle 223 \rangle n = A,T,C or G
<400> 392
atattgttta actectteet ttatatettt taacatttte atggngaaag gtteacatet 60
agteteaett nggenagngn eteetaettg agtetettee eeggeetgnn eeagtngnaa 120
antaccanga accgncatgn cttaanaacn ncctggtttn tgggttnntc aatgactgca 180
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tgcagtgcac caccctgtcc actacgtgat gctgtaggat taaagtctca cagtgggcgg 240
ctgaggatac agcgccgcgt cctgtgttgc tggggaa
                                                                   277
<210> 393
<211> 566
<212> DNA
<213> Homo sapiens
<400> 393
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gtgatctaca ttctgaagtt gtctgaaaat gtcttcatga ttaaattcag cctaaacgtt 120
ttgccgggaa cactgcagag acaatgctgt gagtttccaa ccttagccca tctgcgggca 180
qaqaaqqtct aqtttgtcca tcagcattat catgatatca ggactggtta cttggttaag 240
gaggggtcta ggagatctgt cccttttaga gacaccttac ttataatgaa gtatttggga 300
gggtggtttt caaaagtaga aatgtcctgt attccgatga tcatcctgta aacattttat 360
catttattaa tcatccctgc ctgtgtctat tattatattc atatctctac gctggaaact 420
ttctgcctca atgtttactg tgcctttgtt tttgctagtt tgtgttgttg aaaaaaaaa 480
cattetetge etgagtttta atttttgtee aaagttattt taatetatae aattaaaage 540
                                                                   566
ttttgcctat caaaaaaaaa aaaaaa
<210> 394
<211> 384
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(384)
\langle 223 \rangle n = A,T,C or G
<400> 394
gaacatacat gtcccggcac ctgagctgca gtctgacatc atcgccatca cgggcctcgc 60
tgcaaattng gaccgggcca aggctggact gctggagcgt gtgaaggagc tacaggccna 120
gcaggaggac cgggctttaa ggagttttaa gctgagtgtc actgtagacc ccaaatacca 180
tcccaagatt atcgggagaa agggggcagt aattacccaa atccggttgg agcatgacgt 240
gaacatccag tttcctgata aggacgatgg gaaccagccc caggaccaaa ttaccatcac 300
agggtacgaa aagaacacag aagctgccag ggatgctata ctgagaattg tgggtgaact 360
tgagcagatg gtttctgagg acgt
                                                                   384
<210> 395
<211> 399
<212> DNA
<213> Homo sapiens
<400> 395
ggcaaaactg tgtgacctca ataagacctc gcagatccaa ggtcaagtat cagaagtgac 60
tctgaccttg gactccaaga cctacatcaa cagcctggct atattagatg atgagccagt 120
tatcagaggt ttcatcattg cggaaattgt ggagtctaag gaaatcatgg cctctgaagt 180
attcacgtct ttccagtacc ctgagttctc tatagagttg cctaacacag gcagaattgg 240
ccagctactt gtctgcaatt gtatcttcaa gaataccctg gccatccctt tgactgacgt 300
caagttetet ttggaaagee tgggeatete etcaetaeag acetetgaee atgggaeggt 360
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```
399
gcagcctggt gagaccatcc aatcccaaat aaaatgcac
<210> 396
<211> 403
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(403)
\langle 223 \rangle n = A,T,C or G
<400> 396
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gacattttca acttctgctc cagctgctga taaaacaaat catgtgttta gcttgactcc 120
agacaaggac aacctgttcc ttcataactc tctagagaaa aaaaggagtt gttagtagat 180
actaaaaaaa gtggatgaat aatctggata tttttcctaa aaagattcct tgaaacacat 240
taggaaaatg gagggcctta tgatcagaat gctagaatta gtccattgtg ctgaagcagg 300
gtttagggga gggagtgagg gataaaagaa ggaaaaaaag aagagtgaga aaacctattt 360
atcaaagcag gtgctatcac tcaatgttag gccctgctct ttt
                                                                    403
<210> 397
<211> 100
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(100)
<223> n = A,T,C or G
<400> 397
actagtneag tgtggtggaa ttegeggeeg egtegaeeta naaneeatet etatageaaa 60
tccatccccg ctcctggttg gtnacagaat gactgacaaa
                                                                    100
<210> 398
<211> 278
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(278)
<223> n = A, T, C or G
<400> 398
geggeeget egacageagt teegeeageg etegeeeetg ggtggggatg tgetgeaege 60
ccacctggac atctggaagt cagcggcctg gatgaaagag cggacttcac ctggggcgat 120
tcactactgt gcctcgacca gtgaggagag ctggaccgac agcgaggtgg actcatcatg 180
ctccgggcag cccatccacc tgtggcagtt cctcaaggag ttgctactca agccccacag 240
ctatggccgc ttcattangt ggctcaacaa ggagaagg
                                                                    278
```

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<210> 399
<211> 298
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(298)
<223> n = A,T,C or G
<400> 399
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ggggtgceng catggagege atgggegegg geetgggeea eggeatggat egegtggget 120
ccgagatcga gcgcatgggc ctggtcatgg accgcatggg ctccgtggag cgcatgggct 180
ceggeattga gegeatggge cegetgggee tegaceaeat ggeetecane attganegea 240
tgggccagac catggagcgc attggctctg gcgtggagcn catgggtgcc ggcatggg
<210> 400
<211> 548
<212> DNA
<213> Homo sapiens
<400> 400
acatcaacta cttcctcatt ttaaggtatg gcagttccct tcatcccctt ttcctgcctt 60
gtacatgtac atgtatgaaa tttccttctc ttaccgaact ctctccacac atcacaaggt 120
tgagtctctt ttttccacgt ttaaggggcc atggcaggac ttagagttgc gagttaagac 240
tgcagagggc tagagaatta tttcatacag gctttgaggc cacccatgtc acttatcccg 300
tataccetet caccatecee tigietacie igatgeeeee aagaigeaae igggeageta 360
gttggcccca taattctggg cctttgttgt ttgttttaat tacttgggca tcccaggaag 420
ctttccagtg atctcctacc atgggccccc ctcctgggat caagcccctc ccaggccctg 480
tececageee etectgeece ageeeaceeg ettgeettgg tgeteageee teccattggg 540
                                                                 548
agcaggtt
<210> 401
<211> 355
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(355)
<223> n = A, T, C \text{ or } G
<400> 401
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tgatgtctcc aagtagtcca ccttcattta actctttgaa actgtatcat ctttgccaag 120
taagagtggt ggcctatttc agctgctttg acaaaatgac tggctcctga cttaacgttc 180
tataaatgaa tgtgctgaag caaagtgccc atggtggcgg cgaagaagan aaagatgtgt 240
tttgttttgg actctctgtg gtcccttcca atgctgnggg tttccaacca ggggaagggt 300
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```
cccttttgca ttgccaagtg ccataaccat gagcactact ctaccatggn tctgc
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<210> 402
<211> 407
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(407)
<223> n = A,T,C or G
<400> 402
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tctcacatgc ggtggcatac ataggctcaa aataaaggaa tggagaaaaa tatttcaagc 120
aaatggaaaa cagaaaaaag caggtgttgc actcctactt tctgacaaaa cagactatgc 180
gaataaagat aaaaaagaga aggacattac aaaggtggtc ctgacctttg ataaatctca 240
ttqcttqata ccaacctqqq ctqttttaat tqcccaaacc aaaaqqataa tttqctqaqq 300
ttqtqqaqct tctcccctqc agagagtccc tgatctccca aaatttggtt gagatgtaag 360
gntgattttg ctgacaactc cttttctgaa gttttactca tttccaa
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<210> 403
<211> 303
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(303)
<223> n = A, T, C or G
<400> 403
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tcctaagcaa gagccatggc atggtgaaaa tgcaaaagga gagtctggcc aatctacaaa 120
tagagaacaa gacctactca gtcatgaaca aaaaggcaga caccaacatg gatctcatgg 180
gggattggat attgtaatta tagagcagga agatgacagt gatcgtcatt tggcacaaca 240
tottaacaac gaccgaaacc cattatttac ataaacctcc atteggtaac catgttgaaa 300
                                                                   303
gga
<210> 404
<211> 225
<212> DNA
<213> Homo sapiens
<400> 404
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attgttaatg cactcattta cctttacatg gtgaaagttc tctcttgatc ctacaaacag 120
acattttcca ctcqtqtttc cataqttqtt aaqtqtatca qatqtqttqq qcatqtqaat 180
ctccaagtgc ctgtgtaata aataaagtat ctttatttca ttcat
                                                                   225
```

<210> 405

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<211> 334
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (334)
<223> n = A,T,C or G
<400> 405
gagetgttat actgtgagtt ctactaggaa atcatcaaat ctgagggttg tctggaggac 60
ttcaatacac ctcccccat agtgaatcag cttccagggg gtccagtccc tctccttact 120
teatececat eccatgeeaa aggaagaeee teeeteettg geteaeagee ttetetagge 180
ttcccagtgc ctccaggaca gagtgggtta tgttttcagc tccatccttg ctgtgagtgt 240
ctggtgcggt tgtgcctcca gcttctgctc agtgcttcat ggacagtgtc cagcccatgt 300
cactetecae teteteanng tggateceae ceet
                                                                    334
<210> 406
<211> 216
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(216)
\langle 223 \rangle n = A,T,C or G
<400> 406
tttcatacct aatgagggag ttganatnac atnnaaccag gaaatgcatg gatctcaang 60
qaaacaaaca cccaataaac tcggagtggc agactgacaa ctgtgagaca tgcacttgct 120
acnaaacaca aatttnatgt tgcacccttg tttctacacc tgtgggttat gacaaagaca 180
actgccaaag aatnttcaag aaggaggact gccant
                                                                    216
<210> 407
<211> 413
<212> DNA
<213> Homo sapiens
<400> 407
gctgacttgc tagtatcatc tgcattcatt gaagcacaag aacttcatgc cttgactcat 60
gtaaatgcaa taggattaaa aaataaattt gatatcacat ggaaacagac aaaaaatatt 120
gtacaacatt gcacccagtg tcagattcta cacctggcca ctcaggaagc aagagttaat 180
cccagaggtc tatgtcctaa tgtgttatgg caaatggatg tcatgcacgt accttcattt 240
ggaaaattgt catttgtcca tgtgacagtt gatacttatt cacatttcat atgggcaacc 300
tgccagacag gagaaagtct tcccatgtta aaagacattt attatcttgt tttcctgtca 360
tgggagttcc agaaaaagtt aaaacagaca atgggccagg ttctgtagta aag
                                                                    413
<210> 408
<211> 183
<212> DNA
<213> Homo sapiens
```

```
<220>
<221> misc feature
<222> (1) ... (183)
\langle 223 \rangle n = A,T,C or G
<400> 408
ggagctngcc ctcaattcct ccatntctat gttancatat ttaatgtctt ttgnnattaa 60
tncttaacta qttaatcctt aaagggctan ntaatcctta actagtccct ccattgtgag 120
cattatectt ecagtatten cettetnttt tatttaetee tteetggeta eccatgtaet 180
                                                                    183
ntt
<210> 409
<211> 250
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(250)
<223> n = A, T, C or G
<400> 409
cccacqcatq ataaqctctt tatttctgta agtcctgcta ggaaatcatc aaatctgacg 60
gtggtttggg ggacctgaac aaacctcctg taattaatca gctttcagtt tctccccta 120
qtccctcctt caacaacata ggaggatcct ccccttcttt ctgctcacgg ccttatctag 180
gcttcccagt gcccccagga cagcgtgggc tatgtttaca gcgcntcctt gctggggggg 240
                                                                    250
ggccntatgc
<210> 410
<211> 306
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(306)
<223> n = A, T, C or G
<400> 410
ggctggtttg caagaatgaa atgaatgatt ctacagctag gacttaacct tgaaatggaa 60
aqtcttgcaa tcccatttgc aggatccgtc tgtgcacatg cctctgtaga gagcagcatt 120
cccaqqqacc ttqqaaacaq ttqqcactqt aaqqtqcttq ctccccaaqa cacatcctaa 180
aaggtgttgt aatggtgaaa accgcttcct tctttattgc cccttcttat ttatgtgaac 240
nactggttgg ctttttttgn atcttttta aactggaaag ttcaattgng aaaatgaata 300
                                                                    306
tcntgc
<210> 411
<211> 261
<212> DNA
<213> Homo sapiens
```

```
<220>
<221> misc feature
<222> (1) ... (261)
<223> n = A,T,C or G
<400> 411
agagatattn cttaggtnaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatcttttg tatttaagga ttctgagatt ttgcttgagc aggattagat aaggctgttc 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttacccat cagttccagc 240
cttctctcaa ggngaggcaa a
<210> 412
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (241)
<223> n = A, T, C or G
<400> 412
qttcaatqtt acctgacatt tctacaacac cccactcacc gatgtattcg ttgcccagtg 60
qqaacatacc agcctgaatt tggaaaaaat aattgtgttt cttgcccagg aaatactacg 120
actgactttg atggctccac aaacataacc cagtgtaaaa acagaagatg tggaggggag 180
ctgggagatt tcactgggta cattgaattc ccaaactacc cangcaatta cccagccaac 240
                                                                    241
<210> 413
<211> 231
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(231)
<223> n = A,T,C or G
<400> 413
aactettaca atecaagtga eteatetgtg tgettgaate etttecaetg teteatetee 60
ctcatccaag tttctagtac cttctctttg ttgtgaagga taatcaaact gaacaacaaa 120
aaqtttactc tcctcatttg gaacctaaaa actctcttct tcctgggtct gagggctcca 180
agaatccttg aatcanttct cagatcattg gggacaccan atcaggaacc t
<210> 414
<211> 234
<212> DNA
<213> Homo sapiens
```

```
<400> 414
actgtccatg aagcactgag cagaagctgg aggcacaacg caccagacac tcacagcaag 60
gatggagctg aaaacataac ccactctgtc ctggaggcac tgggaagcct agagaaggct 120
gtgagccaag gagggagggt cttcctttgg catgggatgg ggatgaagta aggagaggga 180
ctggaccccc tggaagctga ttcactatgg ggggaggtgt attgaagtcc tcca
<210> 415
<211> 217
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(217)
<223> n = A, T, C or G
<400> 415
gcataggatt aagactgagt atcttttcta cattctttta actttctaag gggcacttct 60
caaaacacag accaggtagc aaatctccac tgctctaagg ntctcaccac cactttctca 120
cacctagcaa tagtagaatt cagtcctact tctgaggcca gaagaatggt tcagaaaaat 180
antggattat aaaaaataac aattaagaaa aataatc
                                                                    217
<210> 416
<211> 213
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(213)
<223> n = A, T, C \text{ or } G
<400> 416
atgcatatnt aaagganact gcctcgcttt tagaagacat ctggnctgct ctctgcatga 60
ggcacagcag taaagctctt tgattcccag aatcaagaac tctccccttc agactattac 120
cgaatgcaag gtggttaatt gaaggccact aattgatgct caaatagaag gatattgact 180
atattggaac agatggagtc tctactacaa aag
                                                                    213
<210> 417
<211> 303
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(303)
<223> n = A,T,C or G
<400> 417
nagtetteag geceateagg gaagtteaca etggagagaa gteatacata tgtaetgtat 60
gtgggaaagg ctttactctg agttcaaatc ttcaagccca tcagagagtc cacactggag 120
```

```
agaagccata caaatgcaat gagtgtggga agagcttcag gagggattcc cattatcaag 180
ttcatctagt ggtccacaca ggagagaaac cctataaatg tgagatatgt gggaagggct 240
tcantcaaag ttcgtatctt caaatccatc ngaaggncca cagtatanan aaacctttta 300
                                                                    303
agt
<210> 418
<211> 328
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(328)
<223> n = A, T, C \text{ or } G
<400> 418
tttttggcgg tggtggggca gggacgggac angagtctca ctctgttgcc caggctggag 60
tgcacaggca tgatctcggc tcactacaac ccctgcctcc catgtccaag cgattcttgt 120
gcctcagcct tccctgtagc tagaattaca ggcacatgcc accacaccca gctagttttt 180
gtatttttag tagagacagg gtttcaccat gttggccagg ctggtctcaa actcctnacc 240
teagnggtea ggetggtete aaacteetga eetcaagtga tetgeecaee teageeteee 300
                                                                    328
aaagtgctan gattacaggc cgtgagcc
<210> 419
<211> 389
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(389)
<223> n = A, T, C or G
<400> 419
cctcctcaag acggcctgtg gtccgcctcc cggcaaccaa gaagcctgca gtgccatatg 60
acccctgagc catggactgg agcctgaaag gcagcgtaca ccctgctcct gatcttgctg 120
cttgtttcct ctctgtggct ccattcatag cacagttgtt gcactgaggc ttgtgcaggc 180
cgagcaaggc caagctggct caaagagcaa ccagtcaact ctgccacggt gtgccaggca 240
ceggttetec agecaceaac eteacteget eeegcaaatg geacateagt tettetacee 300
taaaggtagg accaaagggc atctgctttt ctgaagtcct ctgctctatc agccatcacg 360
                                                                    389
tggcagccac tcnggctgtg tcgacgcgg
<210> 420
<211> 408
<212> DNA
<213> Homo sapiens
<400> 420
gttcctccta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagcett agcettgget tettgtttet getttttte tggctagace 120
gaagtgtact agccaaggag ttgaagtttg tgactttggt gtttcggcat ggagaccgaa 180
```

```
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attettgaat gagteetata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg aagtgctatg acaaacctgg caagcccg
                                                                    408
<210> 421
<211> 352
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(352)
\langle 223 \rangle n = A,T,C or G
<400> 421
gctcaaaaat ctttttactg atnggcatgg ctacacaatc attgactatt acggaggcca 60
gaggagaatg aggcctggcc tgggagccct gtgcctacta naagcacatt agattatcca 120
ttcactgaca gaacaggtct tttttgggtc cttcttctcc accacnatat acttgcagtc 180
ctccttcttg aagattcttt ggcagttgtc tttgtcataa cccacaggtg tagaaacaag 240
ggtgcaacat gaaatttctg tttcgtagca agtgcatgtc tcacaagttg gcangtctgc 300
cactccgagt ttattgggtg tttgtttcct ttgagatcca tgcatttcct gg
<210> 422
<211> 337
<212> DNA
<213> Homo sapiens
<400> 422
atgccaccat gctggcaatg cagcgggcgg tcgaaggcct gcatatccag cccaagctgg 60
cgatgatcga cggcaaccgt tgcccgaagt tgccgatgcc agccgaagcg gtggtcaagg 120
gegatageaa ggtgeeggeg ategeggegg egteaateet ggeeaaggte ageegtgate 180
gtgaaatggc agctgtcgaa ttgatctacc cgggttatgg catcggcggg cataagggct 240
atcogacaco ggtgcacctg gaagcottgc agoggctggg gccgacgccg attcaccgac 300
gettetteeg eeggtaegge tggeetatga aaattat
                                                                    337
<210> 423
<211> 310
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(310)
<223> n = A, T, C \text{ or } G
<400> 423
gctcaaaaat ctttttactg atatggcatg gctacacaat cattgactat tagaggccag 60
aggagaatga ggcctggcct gggagccctg tgcctactan aagcncatta gattatccat 120
tcactgacag aacaggtctt ttttgggtcc ttcttctcca ccacgatata cttgcagtcc 180
```

teettettga agattetttg geagttgtet ttgteataac ceacaggtgt anaaacaagg 240

```
gtgcaacatg aaatttctgt ttcgtagcaa gtgcatgtct cacagttgtc aagtctgccc 300
                                                                310
tccgagttta
<210> 424
<211> 370
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (370)
<223> n = A,T,C or G
<400> 424
gctcaaaaat ctttttactg ataggcatgg ctacacaatc attgactatt agaggccaga 60
ggagaatgag gcctggcctg ggagccctgt gcctactaga agcacattag attatccatt 120
cactgacaga acaggtettt tttgggteet tetteteeac cacgatatae ttgcagteet 180
ccttcttgaa gattctttgg cagttgtctt tgtcataacc cacaggtgta gaaacatcct 240
ggttgaatct cctggaactc cctcattagg tatgaaatag catgatgcat tgcataaagt 300
cacgaaggtg gcaaagatca caacgctgcc cagganaaca ttcattgtga taagcaggac 360
                                                                370
tccgtcgacg
<210> 425
<211> 216
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(216)
<223> n = A, T, C or G
<400> 425
taacaacnca acatcaaggn aaananaaca ggaatggntg actntgcata aatnggccga 120
anattateca ttatnttaag ggttgaette aggntaeage acacagaeaa acatgeecag 180
gaggntntca ggaccgctcg atgtnttntg aggagg
                                                                216
<210> 426
<211> 596
<212> DNA
<213> Homo sapiens
<400> 426
cttccagtga ggataaccct gttgccccgg gccgaggttc tccattaggc tctgattgat 60
tggcagtcag tgatggaagg gtgttctgat cattccgact gccccaaggg tcgctggcca 120
gctctctgtt ttgctgagtt ggcagtagga cctaatttgt taattaagag tagatggtga 180
gctgtccttg tattttgatt aacctaatgg ccttcccagc acgactcgga ttcagctgga 240
gacatcacgg caacttttaa tgaaatgatt tgaagggcca ttaagaggca cttcccgtta 300
ttaggcagtt catctgcact gataacttct tggcagctga gctggtcgga gctgtggccc 360
aaacgcacac ttggcttttg gttttgagat acaactctta atcttttagt catgcttgag 420
```

<212> DNA

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ggtggatggc cttttcagct ttaacccaat ttgcactgcc ttggaagtgt agccaggaga 480
atacactcat atactcgtgg gcttagaggc cacagcagat gtcattggtc tactgcctga 540
gtcccgctgg tcccatccca ggaccttcca tcggcgagta cctggggagcc cgtgct
<210> 427
<211> 107
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(107)
<223> n = A,T,C or G
<400> 427
gaagaattca agttaggttt attcaaaggg cttacngaga atcctanacc caggncccag 60
cccgggagca gccttanaga gctcctgttt gactgcccgg ctcagng
<210> 428
<211> 38
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(38)
<223> n = A,T,C or G
<400> 428
                                                                   38
gaacttccna anaangactt tattcactat tttacatt
<210> 429
<211> 544
<212> DNA
<213> Homo sapiens
<400> 429
ctttgctgga cggaataaaa gtggacgcaa gcatgacctc ctgatgaggg cgctgcattt 60
attgaagagc ggctgcagcc ctgcggttca gattaaaatc cgagaattgt atagacgccg 120
atatccacga actcttgaag gactttctga tttatccaca atcaaatcat cggttttcag 180
tttggatggt ggctcatcac ctgtagaacc tgacttggcc gtggctggaa tccactcgtt 240
geetteeact teagttacae eteacteace atcetetect gttggttetg tgetgettea 300
agatactaag cccacatttg agatgcagca gccatctccc ccaattcctc ctgtccatcc 360
tgatgtgcag ttaaaaaatc tgccctttta tgatgtcctt gatgttctca tcaagcccac 420
gagtttagtt caaagcagta ttcagcgatt tcaagagaag ttttttattt ttgctttgac 480
acctcaacaa gttagagaga tatgcatatc cagggatttt ttgccaggtg gtaggagaga 540
                                                                   544
ttat
<210> 430
<211> 507
```

```
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(507)
\langle 223 \rangle n = A,T,C or G
<400> 430
cttatcncaa tggggctccc aaacttggct gtgcagtgga aactccgggg gaattttgaa 60
gaacactgac acccatcttc caccccgaca ctctgattta attgggctgc agtgagaaca 120
gagcatcaat ttaaaaagct gcccagaatg ttntcctggg cagcgttgtg atctttgccn 180
ccttcgtgac tttatgcaat gcatcatgct atttcatacc taatgaggga gttccaggag 240
attcaaccag gatgtttcta cncctgtggg ttatgacaaa gacaactgcc aaagaatntt 300
caagaaggag gactgcaagt atatcgtggt ggagaagaag gacccaaaaa agacctgttc 360
tgtcagtgaa tggataatct aatgtgcttc tagtaggcac agggctccca ggccaggcct 420
catteteete tggeetetaa tagteaatga ttgtgtagee atgeetatea gtaaaaagat 480
                                                                    507
ttttgagcaa aaaaaaaaa aaaaaaa
<210> 431
<211> 392
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(392)
\langle 223 \rangle n = A,T,C or G
<400> 431
qaaaattcag aatggataaa aacaaatgaa gtacaaaata tttcagattt acatagcgat 60
aaacaagaaa gcacttatca ggaggactta caaatggaag tacactctan aaccatcatc 120
tatcatggct aaatgtgaga ttagcacagc tgtattattt gtacattgca aacacctaga 180
aagagatggg aaacaaaatc ccaggagttt tgtgtgtgga gtcctgggtt ttccaacaga 240
catcattcca gcattctgag attagggnga ttggggatca ttctggagtt ggaatgttca 300
acaaaagtga tgttgttagg taaaatgtac aacttctgga tctatgcaga cattgaaggt 360
                                                                    392
gcaatgagtc tggcttttac tctgctgttt ct
<210> 432
<211> 387
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(387)
<223> n = A, T, C or G
<400> 432
ggtatccnta cataatcaaa tatagctgta gtacatgttt tcattggngt agattaccac 60
aaatgcaagg caacatgtgt agatctcttg tcttattctt ttgtctataa tactgtattg 120
ngtagtccaa gctctcggna gtccagccac tgngaaacat gctcccttta gattaacctc 180
```

```
qtqqacnctn ttgttgnatt gtctgaactg tagngccctg tattttgctt ctgtctgnga 240
attctgttgc ttctggggca tttccttgng atgcagagga ccaccacaca gatgacagca 300
atctqaattq ntccaatcac agctgcgatt aagacatact gaaatcgtac aggaccggga 360
                                                                   387
acaacgtata gaacactgga gtccttt
<210> 433
<211> 281
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (281)
<223> n = A, T, C or G
<400> 433
ttcaactagc anagaanact gcttcagggn gtgtaaaatg aaaggcttcc acgcagttat 60
ctgattaaag aacactaaga gagggacaag gctagaagcc gcaggatgtc tacactatag 120
caqqcnctat ttqqqttqqc tggaggagct gtggaaaaca tggagagatt ggcgctggag 180
ategeegtgg ctatteeten ttgntattae aceagngagg ntetetgtnt geecactggt 240
tnnaaaaccg ntatacaata atgatagaat aggacacaca t
                                                                   281
<210> 434
<211> 484
<212> DNA
<213> Homo sapiens
<400> 434
ttttaaaata agcatttagt gctcagtccc tactgagtac tctttctctc ccctcctctg 60
aatttaattc tttcaacttg caatttgcaa ggattacaca tttcactgtg atgtatattg 120
tqttqcaaaa aaaaaaaqt gtctttgttt aaaattactt ggtttgtgaa tccatcttgc 180
tttttcccca ttggaactag tcattaaccc atctctgaac tggtagaaaa acatctgaag 240
aqctaqtcta tcaqcatctg acaggtgaat tggatggttc tcagaaccat ttcacccaga 300
cagoctgttt ctatoctgtt taataaatta gtttgggttc tctacatgca taacaaaccc 360
tqctccaatc tqtcacataa aagtctgtga cttgaagttt agtcagcacc cccaccaaac 420
tttatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataaag tacccatgtc 480
                                                                   484
ttta
<210> 435
<211> 424
<212> DNA
<213> Homo sapiens
<400> 435
gegeegetea gageaggtea etttetgeet teeaegteet eetteaagga ageeecatgt 60
gggtagettt caatategea ggttettaet eetetgeete tataagetea aacceaceaa 120
cgatcgggca agtaaacccc ctccctcgcc gacttcggaa ctggcgagag ttcagcgcag 180
atgggcctgt ggggagggg caagatagat gagggggagc ggcatggtgc ggggtgaccc 240
cttggagaga ggaaaaaggc cacaagaggg gctgccaccg ccactaacgg agatggccct 300
ggtagagace tttgggggte tggaacetet ggaeteecea tgetetaaet eecacaetet 360
```

gctatcagaa acttaaactt gaggattttc tctgtttttc actcgcaata aattcagagc 420

```
424
aaac
<210> 436
<211> 667
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(667)
<223> n = A, T, C \text{ or } G
<400> 436
accttgggaa nactctcaca atataaaggg tcgtagactt tactccaaat tccaaaaagg 60
tectggeeat gtaateetga aagtttteee aaggtageta taaaateett ataagggtge 120
agcetettet ggaatteete tgattteaaa gteteaetet caagttettg aaaacgaggg 180
cagttcctga aaggcaggta tagcaactga tcttcagaaa gaggaactgt gtgcaccggg 240
atgggctgcc agagtaggat aggattccag atgctgacac cttctggggg aaacagggct 300
gccaggtttg tcatagcact catcaaagtc cggtcaacgt ctgtgcttcg aatataaacc 360
tgttcatgtt tataggactc attcaagaat tttctatatc tctttcttat atactctcca 420
agttcataat gctgctccat gcccagctgg gtgagttggc caaatccttg tggccatgag 480
gatteettta tggggteagt gggaaaggtg teaatgggae tteggtetee atgeegaaae 540
accaaagtca caaacttcaa ctccttggct agtacacttc ggtctagcca gaaaaaaagc 600
agaaacaaga agccaaggct aaggcttgct gccctgccag gaggaggggt gcagctctca 660
                                                                   667
tgttgag
<210> 437
<211> 693
<212> DNA
<213> Homo sapiens
<400> 437
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acacagccag gtaaggaaag ctggattggc acactaggac tctaccatac cgggttttgt 120
taaagctcag gttaggaggc tgataagctt ggaaggaact tcagacagct ttttcagatc 180
ataaaaqata attottaqoo catqttotto tocagagoag acctgaaatg acagoacago 240
aggtactect ctattttcac ceetettget tetaetetet ggeagteaga eetgtgggag 300
gccatgggag aaagcagctc tctggatgtt tgtacagatc atggactatt ctctgtggac 360
catttctcca ggttacccta ggtgtcacta ttggggggac agccagcatc tttagctttc 420
atttgagttt ctgtctgtct tcagtagagg aaacttttgc tcttcacact tcacatctga 480
acacctaact gctgttgctc ctgaggtggt gaaagacaga tatagagctt acagtattta 540
tcctatttct aggcactgag ggctgtgggg taccttgtgg tgccaaaaca gatcctgttt 600
taaggacatg ttgcttcaga gatgtctgta actatctggg ggctctgttg gctctttacc 660
                                                                    693
ctgcatcatg tgctctcttg gctgaaaatg acc
<210> 438
<211> 360
<212> DNA
<213> Homo sapiens
<400> 438
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ctgcttatca caatgaatgt tctcctgggc agcgttgtga tctttgccac cttcgtgact 60
ttatgcaatg catcatgcta tttcatacct aatgagggag ttccaggaga ttcaaccagg 120
atgtttctac acctgtgggt tatgacaaag acaactgcca aagaatcttc aagaaggagg 180
actgcaagta tatctggtgg agaagaagga cccaaaaaag acctgttctg tcagtgaatg 240
gataatctaa tgtgcttcta gtaggcacag ggctcccagg ccaggcctca ttctcctctg 300
gcctctaata gtcaataatt gtgtagccat gcctatcagt aaaaagattt ttgagcaaac 360
<210> 439
<211> 431
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (431)
\langle 223 \rangle n = A,T,C or G
<400> 439
qttcctnnta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagcctt agccttggct tcttgtttct gctttttttc tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgactttggt gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attettgaat gagteetata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
aatttagtag t
<210> 440
<211> 523
<212> DNA
<213> Homo sapiens
<400> 440
agagataaag cttaggtcaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatcttttg tatttaagga ttctgagatt ttgcttgagc aggattagat aaggctgttc 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttacccat cagttccagc 240
cttctctcaa ggagaggcaa agaaaggaga tacagtggag acatctggaa agttttctcc 300
actggaaaac tgctactatc tgtttttata tttctgttaa aatatatgag gctacagaac 360
taaaaattaa aacctctttg tgtcccttgg tcctggaaca tttatgttcc ttttaaagaa 420
acaaaaatca aactttacag aaagatttga tgtatgtaat acatatagca gctcttgaag 480
                                                                   523
tatatatatc atagcaaata agtcatctga tgagaacaag cta
<210> 441
<211> 430
<212> DNA
<213> Homo sapiens
<400> 441
gttcctccta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagcett agcettgget tettgtttet getttttte tggctagaec 120
```

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gaaqtgtact agccaaggag ttgaagtttg tgactttggt gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
qccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attettgaat gagteetata aacatgaaca ggtttatatt egaageacag 360
acqttqaccq gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
                                                                   430
aatttagtag
<210> 442
<211> 362
<212> DNA
<213> Homo sapiens
<400> 442
ctaaggaatt agtagtgttc ccatcacttg tttggagtgt gctattctaa aagattttga 60
tttcctqqaa tgacaattat attttaactt tggtggggga aagagttata ggaccacagt 120
cttcacttct gatacttgta aattaatctt ttattgcact tgttttgacc attaagctat 180
atgtttagaa atggtcattt tacggaaaaa ttagaaaaat tctgataata gtgcagaata 240
aatgaattaa tgttttactt aatttatatt gaactgtcaa tgacaaataa aaattctttt 300
tgattatttt ttgttttcat ttaccaqaat aaaaactaag aattaaaagt ttgattacag 360
tc
                                                                   362
<210> 443
<211> 624
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (624)
<223> n = A,T,C or G
<400> 443
tttttttttt qcaacacaat atacatcaca gtgaaatgtg taatccttgc aaattgcaag 60
ttgaaagaat taaattcaga ggaggggaga gaaagagtac tcagtaggga ctgagcacta 120
aatgettatt ttaaaagaaa tgtaaagage agaaageaat teaggetaee etgeettttg 180
tqctqqctaq tactccqqtc qqtqtcaqca gcacqtggca ttgaacattg caatqtggag 240
cccaaaccac agaaaatggg gtgaaattgg ccaactttct attaacttgg cttcctgttt 300
tataaaatat tgtgaataat atcacctact tcaaagggca gttatgaggc ttaaaatgaac 360
taacgcctac aaaacactta aacatagata acataggtgc aagtactatg tatctggtac 420
atggtaaaca toottattat taaagtcaac gotaaaatga atgtgtgtgc atatgctaat 480
agtacagaga gagggcactt aaaccaacta agggcctgga gggaaggttt cctggaaaga 540
ngatgcttgt gctgggtcca aatcttggtc tactatgacc ttggccaaat tatttaaact 600
ttgtccctat ctgctaaaca gatc
                                                                   624
<210> 444
<211> 425
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
```

```
<222> (1) ... (425)
<223> n = A, T, C \text{ or } G
<400> 444
gcacatcatt nntcttgcat tctttgagaa taagaagatc agtaaatagt tcagaagtgg 60
qaaqetttqt ccaggectqt gtgtgaacce aatgttttge ttagaaatag aacaagtaag 120
ttcattgcta tagcataaca caaaatttgc ataagtggtg gtcagcaaat ccttgaatgc 180
tgcttaatgt gagaggttgg taaaatcctt tgtgcaacac tctaactccc tgaatgtttt 240
gctgtgctgg gacctgtgca tgccagacaa ggccaagctg gctgaaagag caaccagcca 300
cctctgcaat ctgccacctc ctgctggcag gatttgtttt tgcatcctgt gaagagccaa 360
ggaggcacca gggcataagt gagtagactt atggtcgacg cggccgcgaa tttagtagta 420
                                                                    425
gtaga
<210> 445
<211> 414
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (414)
<223> n = A, T, C or G
<400> 445
catqtttatg nttttggatt actttgggca cctagtgttt ctaaatcgtc tatcattctt 60
ttctgttttt caaaagcaga gatggccaga gtctcaacaa actgtatctt caagtctttg 120
tgaaattett tgeatgtgge agattattgg atgtagttte etttaaetag catataaate 180
tggtgtgttt cagataaatg aacagcaaaa tgtggtggaa ttaccatttg gaacattgtg 240
aatgaaaaat tgtgtctcta gattatgtaa caaataacta tttcctaacc attgatcttt 300
qqatttttat aatcctactc acaaatgact aggcttctcc tcttgtattt tgaagcagtg 360
tgggtgctgg attgataaaa aaaaaaaaag tcgacgcggc cgcgaattta gtag
                                                                    414
<210> 446
<211> 631
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(631)
\langle 223 \rangle n = A,T,C or G
<400> 446
acaaattaga anaaagtgcc agagaacacc acataccttg tccggaacat tacaatggct 60
tctgcatgca tgggaagtgt gagcattcta tcaatatgca ggagccatct tgcaggtgtg 120
atqctqqtta tactggacaa cactgtgaaa aaaaggacta cagtgttcta tacgttgttc 180
ccqqtcctqt acqatttcag tatgtcttaa tcgcagctgt gattggaaca attcagattg 240
ctqtcatctq tqtqqtqqtc ctctqcatca caaqqqccaa actttagqta atagcattgg 300
actgagattt gtaaactttc caaccttcca ggaaatgccc cagaagcaac agaattcaca 360
gacagaagca aaatacaggg cactacagtt cagacaatac aacaagagcg tccacgaggt 420
taatctaaag ggagcatgtt tcacagtggc tggactaccg agagcttgga ctacacaata 480
```

```
cagtattata gacaaaagaa taagacaaga gatctacaca tgttgccttg catttgtggt 540
aatctacacc aatqaaaaca tgtactacag ctatatttga ttatgtatgg atatatttga 600
aatagtatac attgtcttga tgttttttct g
<210> 447
<211> 585
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (585)
<223> n = A, T, C or G
<400> 447
ccttgggaaa antntcacaa tataaagggt cgtagacttt actccaaatt ccaaaaaggt 60
cctqqccatq taatcctgaa agttttccca aggtagctat aaaatcctta taagggtgca 120
qcctcttctg gaattcctct gatttcaaag tctcactctc aagttcttga aaacgagggc 180
agttcctgaa aggcaggtat agcaactgat cttcagaaag aggaactgtg tgcaccggga 240
tqqqctqcca gagtaggata ggattccaga tgctgacacc ttctggggga aacagggctg 300
ccaggtttgt catagcactc atcaaagtcc ggtcaacgtc tgtgcttcga atataaacct 360
gttcatgttt ataggactca ttcaagaatt ttctatatct ctttcttata tactctccaa 420
gttcataatg ctgctccatg cccagctggg tgagttggcc aaatccttgt ggccatgagg 480
attectttat ggggteagtg ggaaaggtgt caatgggact teggteteea tgeegaaaca 540
                                                                     585
ccaaagtcac aaacttcaac tccttggcta gtacacttcg gtcta
<210> 448
<211> 93
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(93)
\langle 223 \rangle n = A,T,C or G
<400> 448
tgctcgtggg tcattctgan nnccgaactg accntgccag ccctgccgan gggccnccat 60
ggctccctag tgccctggag agganggggc tag
                                                                     93
<210> 449
<211> 706
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(706)
\langle 223 \rangle n = A,T,C or G
<400> 449
```

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ccaagttcat gctntgtgct ggacgctgga cagggggcaa aagcnnttgc tcgtgggtca 60
ttctgancac cgaactgacc atgccagccc tgccgatggt cctccatggc tccctagtgc 120
cctggagagg aggtgtctag tcagagagta gtcctggaag gtggcctctg ngaggagcca 180
eggggacage atcetgcaga tggtegggeg egteceatte gccattcagg etgegcaact 240
gttgggaagg gcgatcggtg cgggcctctt cgctattacg ccagctggcg aaagggggat 300
gtgctgcaag gcgattaagt tgggtaacgc cagggttttc ccagtcncga cgttgtaaaa 360
cgacggccag tgaattgaat ttaggtgacn ctatagaaga gctatgacgt cgcatgcacg 420
cgtacgtaag cttggatcct ctagagcggc cgcctactac tactaaattc gcggccgcgt 480
cgacgtggga tccncactga gagagtggag agtgacatgt gctggacnct gtccatgaag 540
cactgagcag aagctggagg cacaacgcnc cagacactca cagctactca ggaggctgag 600
aacaggttga acctgggagg tggaggttgc aatgagctga gatcaggccn ctgcncccca 660
706
<210> 450
<211> 493
<212> DNA
<213> Homo sapiens
<400> 450
gagacggagt gtcactctgt tgcccaggct ggagtgcagc aagacactgt ctaagaaaaa 60
acagttttaa aaggtaaaac aacataaaaa gaaatatcct atagtggaaa taagagagtc 120
aaatgagget gagaacttta caaagggate ttacagacat gtegecaata teactgeatg 180
agcctaagta taagaacaac ctttggggag aaaccatcat ttgacagtga ggtacaattc 240
caagtcaggt agtgaaatgg gtggaattaa actcaaatta atcctgccag ctgaaacgca 300
agagacactg tcagagagtt aaaaagtgag ttctatccat gaggtgattc cacagtcttc 360
tcaagtcaac acatctgtga actcacagac caagttctta aaccactgtt caaactctgc 420
tacacatcag aatcacctgg agagetttac aaacteecat tgeegagggt egaegeggee 480
                                                                 493
gcgaatttag tag
<210> 451
<211> 501
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(501)
<223> n = A, T, C \text{ or } G
<400> 451
gggegegtee cattegeeat teaggetgeg caactgttgg gaagggegat eggtgegge 60
ctcttcgcta ttacgccagc tggcgaaagg gggatgtgct gcaaggcgat taagttgggt 120
aacgccaggg ttttcccagt cncgacgttg taaaacgacg gccagtgaat tgaatttagg 180
tgacnctata gaagagctat gacgtcgcat gcacgcgtac gtaagcttgg atcctctaga 240
geggeegeet actactacta aattegegge egegtegaeg tgggateene actgagagag 300
tggagagtga catgtgctgg acnetgteca tgaagcactg agcagaaget ggaggcacaa 360
cgcnccagac actcacagct actcaggagg ctgagaacag gttgaacctg ggaggtggag 420
gttgcaatga gctgagatca ggccnctgcn ccccagcatg gatgacagag tgaaactcca 480
                                                                 501
tcttaaaaaa aaaaaaaaa a
```

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<211> 51
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(51)
<223> n = A, T, C or G
<400> 452
agacggtttc accnttacaa cnccttttag gatgggnntt ggggagcaag c
                                                                    51
<210> 453
<211> 317
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (317)
<223> n = A, T, C \text{ or } G
<400> 453
tacatcttgc tttttcccca ttggaactag tcattaaccc atctctgaac tggtagaaaa 60
acatctgaag agctagtcta tcagcatctg gcaagtgaat tggatggttc tcagaaccat 120
ttcacccana cagcctgttt ctatcctgtt taataaatta gtttgggttc tctacatgca 180
taacaaaccc tgctccaatc tgtcacataa aagtctgtga cttgaagttt antcagcacc 240
cccaccaaac tttattttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataagg 300
                                                                    317
tacccatgtc tttatta
<210> 454
<211> 231
<212> DNA
<213> Homo sapiens
<400> 454
ttcgaggtac aatcaactct cagagtgtag tttccttcta tagatgagtc agcattaata 60
taagccacgc cacgctcttg aaggagtctt gaattctcct ctgctcactc agtagaacca 120
agaagaccaa attcttctgc atcccagctt gcaaacaaaa ttgttcttct aggtctccac 180
cetteettt teagtgttee aaageteete acaattteat gaacaacage t
<210> 455
<211> 231
<212> DNA
<213> Homo sapiens
<400> 455
taccaaagag ggcataataa tcagtctcac agtagggttc accatcctcc aagtgaaaaa 60
cattgttccg aatgggcttt ccacaggcta cacacacaaa acaggaaaca tgccaagttt 120
gtttcaacgc attgatgact tctccaagga tcttcctttg gcatcgacca cattcagggg 180
caaagaattt ctcatagcac agctcacaat acagggctcc tttctcctct a
```

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<210> 456
<211> 231
<212> DNA
<213> Homo sapiens
<400> 456
ttggcaggta cccttacaaa gaagacacca taccttatgc gttattaggt ggaataatca 60
ttccattcag tattatcgtt attattcttg gagaaaccct gtctgtttac tgtaaccttt 120
tgcactcaaa ttcctttatc aggaataact acatagccac tatttacaaa gccattggaa 180
cctttttatt tggtgcagct gctagtcagt ccctgactga cattgccaag t
<210> 457
<211> 231
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(231)
<223> n = A, T, C \text{ or } G
<400> 457
cgaggtaccc aggggtctga aaatctctnn tttantagtc gatagcaaaa ttgttcatca 60
gcattcctta atatgatctt gctataatta gatttttctc cattagagtt catacagttt 120
tatttgattt tattagcaat ctctttcaga agacccttga gatcattaag ctttgtatcc 180
agttgtctaa atcgatgcct catttcctct gaggtgtcgc tggcttttgt g
<210> 458
<211> 231
<212> DNA
<213> Homo sapiens
<400> 458
aggtctggtt cccccactt ccactcccct ctactctctc taggactggg ctgggccaag 60
agaagagggg tggttaggga agccgttgag acctgaagcc ccaccctcta ccttccttca 120
acaccctaac cttgggtaac agcatttgga attatcattt gggatgagta gaatttccaa 180
ggtcctgggt taggcatttt ggggggccag accccaggag aagaagattc t
<210> 459
<211> 231
<212> DNA
<213> Homo sapiens
<400> 459
ggtaccgagg ctcgctgaca cagagaaacc ccaacgcgag gaaaggaatg gccagccaca 60
ccttcgcgaa acctgtggtg gcccaccagt cctaacggga caggacagag agacagagca 120
gccctgcact gttttccctc caccacagcc atcctgtccc tcattggctc tgtgctttcc 180
actatacaca gtcaccgtcc caatgagaaa caagaaggag caccctccac a
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```
<211> 231
<212> DNA
<213> Homo sapiens
<400> 460
gcaggtataa catgctgcaa caacagatgt gactaggaac ggccggtgac atggggaggg 60
cctatcaccc tattcttggg ggctgcttct tcacagtgat catgaagcct agcagcaaat 120
cccacctccc cacacgcaca cggccagcct ggagcccaca gaagggtcct cctgcagcca 180
gtggagcttg gtccagcctc cagtccaccc ctaccaggct taaggataga a
                                                                231
<210> 461
<211> 231
<212> DNA
<213> Homo sapiens
<400> 461
cgaggtttga gaagctctaa tgtgcagggg agccgagaag caggcggcct agggagggtc 60
gcgtgtgctc cagaagagtg tgtgcatgcc agaggggaaa caggcgcctg tgtgtcctgg 120
gtggggttca gtgaggagtg ggaaattggt tcagcagaac caagccgttg ggtgaataag 180
agggggattc catggcactg atagagccct atagtttcag agctgggaat t
<210> 462
<211> 231
<212> DNA
<213> Homo sapiens
<400> 462
aggtaccctc attgtagcca tgggaaaatt gatgttcagt ggggatcagt gaattaaatg 60
gggtcatgca agtataaaaa ttaaaaaaaa aagacttcat gcccaatctc atatgatgtg 120
gaagaactgt tagagagacc aacagggtag tgggttagag atttccagag tcttacattt 180
tctagaggag gtatttaatt tcttctcact catccagtgt tgtatttagg a
                                                                231
<210> 463
<211> 231
<212> DNA
<213> Homo sapiens
<400> 463
actgagtaga caggtgtcct cttggcatgg taagtcttaa gtcccctccc agatctgtga 120
catttgacag gtgtcttttc ctctggacct cggtgtcccc atctgagtga gaaaaggcag 180
tggggaggtg gatcttccag tcgaagcggt atagaagccc gtgtgaaaag c
                                                                231
<210> 464
<211> 231
<212> DNA
<213> Homo sapiens
<400> 464
qtactctaag attttatcta agttgccttt tctgggtggg aaagtttaac cttagtgact 60
aaggacatca catatgaaga atgtttaagt tggaggtggc aacgtgaatt gcaaacaggg 120
```

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cctgcttcag tgactgtgtg cctgtagtcc cagctactcg ggagtctgtg tgaggccagg 180
ggtgccagcg caccagctag atgctctgta acttctaggc cccattttcc c
<210> 465
<211> 231
<212> DNA
<213> Homo sapiens
<400> 465
catgttgttg tagctgtggt aatgctggct gcatctcaga cagggttaac ttcagctcct 60
gtggcaaatt agcaacaaat tctgacatca tatttatggt ttctgtatct ttgttgatga 120
aggatggcac aatttttgct tgtgttcata atatactcag attagttcag ctccatcaga 180
taaactggag acatgcagga cattagggta gtgttgtagc tctggtaatg a
<210> 466
<211> 231
<212> DNA
<213> Homo sapiens
<400> 466
caggtacete tttecattgg atactgtget ageaageatg eteteegggg tttttttaat 60
ggccttcgaa cagaacttgc cacataccca ggtataatag tttctaacat ttgcccagga 120
cctgtgcaat caaatattgt ggagaattcc ctagctggag aagtcacaaa gactataggc 180
aataatggag accagtccca caagatgaca accagtcgtt gtgtgcggct g
<210> 467
<211> 311
<212> DNA
<213> Homo sapiens
<400> 467
gtacaccctg gcacagtcca atctgaactg gttcggcact catctttcat gagatggatg 60
tggtggcttt tctccttttt catcaagact cctcagcagg gagcccagac cagcctgcac 120
tgtgccttaa cagaaggtct tgagattcta agtgggaatc atttcagtga ctgtcatgtg 180
gcatgggtct ctgcccaagc tcgtaatgag actatagcaa ggcggctgtg ggacgtcagt 240
tgtgacctgc tgggcctccc aatagactaa caggcagtgc cagttggacc caagagaaga 300
                                                                   311
ctgcagcaga c
<210> 468
<211> 3112
<212> DNA
<213> Homo sapiens
<400> 468
cattgtgttg ggagaaaaac agaggggaga tttgtgtggc tgcagccgag ggagaccagg 60
aagatctgca tggtgggaag gacctgatga tacagagttt gataggagac aattaaaggc 120
tggaaggcac tggatgcctg atgatgaagt ggactttcaa actggggcac tactgaaacg 180
atgggatggc cagagacaca ggagatgagt tggagcaagc tcaataacaa agtggttcaa 240
cgaggacttg gaattgcatg gagctggagc tgaagtttag cccaattgtt tactagttga 300
gtgaatgtgg atgattggat gatcatttct catctctgag cctcaggttc cccatccata 360
aaatgggata cacagtatga totataaagt gggatatagt atgatotact toactgggtt 420
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                              40
         35
His His His Thr His Glu His Thr Asp Thr Leu Pro Tyr Gly His Trp
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His Thr His Cys His Thr Val Thr Trp Thr His Leu His Thr Ile Thr

75

Pro Pro His Thr Leu Pro Val Asp Thr Arg Thr His Arg His Cys His 85 90 95

Thr Asp Thr Gln Asn Thr Val Thr Arg Arg His His His Ala Asp Thr 100 105 110

Pro Pro Leu Trp Cys Arg Leu Asn Tyr Pro Ala Gly Gly Thr Ala Val

Ala Tyr Ser Cys Leu Ser Asp Trp Leu Ser Pro Gln 130 135 140

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Gly Glu Ile Thr Trp Thr His His His Thr Ile Thr Gly Thr Gln Thr 35 40 45

His Gly Asp Ile Thr Thr Trp Thr His Cys His Thr Thr Thr Gly Thr 50 55 60

Arg Asp Ile Thr Leu Ser His Gly His Thr Ile Thr His Met Asn Thr 65 70 75 80

Pro Thr His Cys His Met Asp Thr Gly Thr His Thr Ala Thr Leu Ser 85 90 95

His Gly His Thr Ser Thr Pro Ser His His His Thr His Cys Leu Trp
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Thr Gln Gly His Thr Asp Thr Val Thr Gln Ile His Lys Thr Leu Ser 115 120 125

His Gly Asp Ile Thr Met Gln Ile His His His Ser Gly Ala Val 130 135 140

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Ser His Glu His Thr Gly Ile Val Thr Trp Thr Asp Thr Gln Thr Tyr 20 25 30

Gly Glu Ile Thr Leu Thr His His His Thr Ile Thr Gly Thr Gln Thr 35 40 45

His Gly Asp Ile Thr Thr Trp Thr His Cys His Thr Thr Thr Gly Thr 50 55 60

Arg Asp Ile Thr Leu Ser His Gly His Thr Ile Thr His Met Asn Thr 65 70 75 80

Pro Thr His Cys His Met Asp Thr Ala Thr His Thr Ala Thr Leu Ser 85 90 95

His Gly His Thr Ser Ile Pro Ser His His His Thr His Cys His Val

Asp Thr Arg Thr His Arg His Cys His Thr Asp Thr Gln Asn Thr Val

Thr Arg Arg His His His Ala Asp Thr Pro Pro His Gly His Ser Thr 130 135 140

Arg His Ser Ala Thr Gln Ile His His His Thr Glu Met Arg Thr His 145 150 155 160

Cys His Thr Asp Thr Thr Thr Ser Leu Pro His Phe His Val Ser Ala 165 170 175

Gly Gly Val Gly Pro Thr Thr Leu Gly Ser Asn Arg Glu Ile Thr Trp 180 185 190

Thr Tyr Ser Glu Gly Lys Ile Phe Phe Tyr Phe Leu Gly Asn Gln Ala 195 200 205

Arg Leu Cys Leu Lys Lys Arg Lys Lys Lys Gln Tyr Thr Val 210 215 220

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Val Gly Phe Leu Val Val Lys Arg Gln Thr Ile Gly Arg Leu Glu Arg 35 40 45

Asp Phe Met Phe Lys Cys Arg Lys Gln Pro Gly Leu Pro Pro Ser Gly 50 55 60

Leu Cys Leu Leu Trp Pro Trp Pro Asn Leu Glu Phe Gly Arg Arg Gln 65 70 75 80

Asp Arg Leu Thr Trp Ser Ser Val Ser Val Ala Gly Val Cys Ala Cys 85 90 95

Arg Ala Arg Pro Gly Trp Leu Gly Glu Gln Pro Ala Thr Ser Ala Gly
100 105 110

Val Arg Leu Glu Gln Val Glu Gln Pro Pro Ala His Pro Leu Gln Glu 115 120 125

Ala Gly Val Ala Arg Phe Pro Arg Pro Glu Trp Val Pro Pro Asn Gly 130 135 140

<210> 481

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<213> Homo sapiens

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Met His Gly Pro Gln Val Leu Ala Arg Cys Ser Glu Cys Ala Cys Pro 5 10 15

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Pro Pro Thr Leu Pro Ser Gln Gly Ser Gly Trp Pro Cys Ser His Ser 35 40 45

Leu Ser Gly Cys His Leu Met Ala Asp Gly Ala Lys Ala Leu Gly Lys 50 55 60

Ala Asp Gly Pro Trp Pro Tyr Leu Phe Val Arg Arg Thr Asp Val Pro 65 70 75 80

- Cys Pro Ala Ala Ser Glu Val Gly Gly Cys Ala Pro Ser Ser Trp Arg 85 90 95
- Ala Leu Ala Glu Val Thr Gly Cys Ser Leu Gly Pro Leu Gly Leu Ala 100 105 110
- Gln His Ala Gln Ala Ser Val Leu Leu Cys Tyr Lys Trp Ser His 115 120 125
- Ile Gly Glu Thr Ser Ser His Leu Arg Ser Lys Val Tyr Ala Ala Phe 130 135 140
- Gly Gly Ser Ser Pro Cys Leu Lys Gly Leu Met Ser Leu Trp Ala Ser 145 150 155 160

Trp Leu Ser Arg Gly Arg Pro 165

<210> 482

<211> 144

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<213> Homo sapiens

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- Pro Cys Leu Trp Gly Ser Ser Pro Cys Leu Arg Cys His Met Ala Leu 20 25 30
- Arg Ala Ser Trp Leu Pro Gly Gly Gly Pro Gln Ala Ile Leu Gly Arg 35 40 45
- Thr Leu Cys Ser Ser Ala Glu Ser Ser Gln Asp Cys His Pro Gly Gly 50 55 60
- Pro Ser Ile Ala Leu Ala Lys Pro Cys Arg Gly Val Trp Leu Leu Phe 65 70 75 80
- Glu Pro Ala Trp Pro Pro Trp His Ala Arg Ala Pro Gly Ala Gly Thr
  85 90 95
- Leu Leu Arg Val Cys Leu Ser Cys Leu Gly Cys His Leu Cys Gly Gly
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- Ala Ser Gly Gly Gly Pro Ala Thr Asn Leu Thr Gln Ser Arg Lys
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Trp Met Ala Met Phe Pro Gln Pro Glu Trp Leu Pro Pro Asp Gly

140

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5 10 15

135

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Gly Phe Leu Val Ala Lys Arg Arg Thr Thr Gly Leu Leu Glu Glu Asp 35 40 45

Phe Thr Phe Lys Cys Arg Lys Gln Pro Lys Leu Pro Ser Met Arg Leu 50 55 60

Ser Leu Leu Trp Pro Trp Arg Asp Leu Lys Phe Val Pro Arg Gln Asp 65 70 75 80

Lys Leu Thr Arg Ser Ser Val Ser Val Ala Gly Ala Tyr Ala Cys Arg 85 90 95

Ala Gly Pro Gly Trp Leu Lys Glu Gln Pro Ala Thr Ser Ala Arg Val

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      <212> DNA
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      <400> 503
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Asn Thr Ala Asn
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      <211> 407
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ctgacaaccg aggacacggc cacctatttc tgtgccagaa atagtgattt tagtggtatg
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acagtetetg gatteteeet cageaactae gacetgaact gggteegeea ggeteeaggg
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gcaaaaggcc ggttcaccat ctccaaaacc tcgaccaccg tggatctcaa gatcgccagt
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Gly
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Pro Pro Pro Pro Ala
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      <211> 20
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      <223> Made in a lab
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      <211> 254
      <212> PRT
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Val Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln
                        55
                                             60
Trp Val Leu Ser Ala Thr His Cys Phe Gln Asn Ser Tyr Thr Ile Gly
                    70
                                        75
Leu Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met
                                    90
Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu
            100
                                105
Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu
                            120
Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala
                        135
                                            140
Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg
                    150
                                        155
Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu
                165
                                    170
Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys
            180
                                185
Ala Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser Gly
                            200
                                                205
Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly
                        215
Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu
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<212> DNA

<213> Homo sapien

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Val Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln
                        55
Trp Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly
                    70
                                        75
Leu Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met
                                    90
                85
Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu
                                105
                                                     110
Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu
                            120
                                                125
Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala
                        135
Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg
                    150
                                        155
Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu
                165
                                    170
                                                         175
Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys
            180
                                185
Ala Gly Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly
                            200
        195
                                                205
Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly
                        215
                                            220
Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu
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Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
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10

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Met Tyr Val Val Ala Met Phe Gly Asn Cys Ile Val Val Phe Ile Val 35 45

Arg Thr Glu Arg Ser Leu His Ala Pro Met Tyr Leu Phe Leu Cys Met 50 55 60

Leu Ala Ala Ile Asp Leu Ala Leu Ser Thr Ser Thr Met Pro Lys Ile 75

Leu Ala Leu Phe Trp Phe Asp Ser Arg Glu Ile Ser Phe Glu Ala Cys 85 90

Leu Thr Gln Met Phe Phe Ile His Ala Leu Ser Ala Ile Glu Ser Thr 100 105 110

Ile Leu Leu Ala Met Ala Phe Asp Arg Tyr Val Ala Ile Cys His Pro 115 120

Leu Arg His Ala Ala Val Leu Asn Asn Thr Val Thr Ala Gln Ile Gly 130 135 140

Ile Val Ala Val Val Arg Gly Ser Leu Phe Phe Phe Pro Leu Pro Leu 145 150 155 160

Leu Ile Lys Arg Leu Ala Phe Cys His Ser Asn Val Leu Ser His Ser 165 170 175

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Pro Asn Val Val Tyr Gly Leu Thr Ala Ile Leu Leu Val Met Gly Val
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Asp Val Met Phe Ile Ser Leu Ser Tyr Phe Leu Ile Ile Arg Thr Val
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Val Ser His Ile Gly Val Val Leu Ala Phe Tyr Val Pro Leu Ile Gly
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                245
Leu Ser Val Val His Arg Phe Gly Asn Ser Leu His Pro Ile Val Arg
            260
                                265
Val Val Met Gly Asp Ile Tyr Leu Leu Pro Pro Val Ile Asn Pro
                            280
Ile Ile Tyr Gly Ala Lys Thr Lys Gln Ile Arg Thr Arg Val Leu Ala
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Val	Lys	Thr 35	Leu	Gly	Ser	Lys	Arg 40	Cys	Lys	Trp	Cys	Cys 45	His	Cys	Ph
Pro	Cys 50	Cys	Arg	Gly	Ser	Gly 55	Lys	Ser	Asn	Val	Val 60	Ala	Trp	Gly	As
Tyr 65	Asp	Asp	Ser	Ala	Phe 70	Met	Asp	Pro	Arg	Tyr 75	His	Val	His	Gly	Gl 8
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Cys Ala Gly Met Arg Leu Arg Val Ala Met Cys His Met Ile Tyr Arg

170

175

- Lys Ala Leu Arg Leu Ser Asn Met Ala Met Gly Lys Thr Thr Thr Gly
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- Gln Ile Val Asn Leu Leu Ser Asn Asp Val Asn Lys Phe Asp Gln Val 195 200 205
- Thr Val Phe Leu His Phe Leu Trp Ala Gly Pro Leu Gln Ala Ile Ala 210 215 220
- Val Thr Ala Leu Leu Trp Met Glu Ile Gly Ile Ser Cys Leu Ala Gly 225 230 235 240
- Met Ala Val Leu Ile Ile Leu Leu Pro Leu Gln Ser Cys Phe Gly Lys
  245 250 255
- Leu Phe Ser Ser Leu Arg Ser Lys Thr Ala Thr Phe Thr Asp Ala Arg 260 265 270
- Ile Arg Thr Met Asn Glu Val Ile Thr Gly Ile Arg Ile Ile Lys Met 275 280 285
- Tyr Ala Trp Glu Lys Ser Phe Ser Asn Leu Ile Thr Asn Leu Arg Lys 290 295 300
- Lys Glu Ile Ser Lys Ile Leu Arg Ser Ser Cys Leu Arg Gly Met Asn 305 310 315 320
- Leu Ala Ser Phe Phe Ser Ala Ser Lys Ile Ile Val Phe Val Thr Phe 325 330 335
- Thr Thr Tyr Val Leu Leu Gly Ser Val Ile Thr Ala Ser Arg Val Phe 340 345 350
- Val Ala Val Thr Leu Tyr Gly Ala Val Arg Leu Thr Val Thr Leu Phe 355 360 365
- Phe Pro Ser Ala Ile Glu Arg Val Ser Glu Ala Ile Val Ser Ile Arg 370 375 380
- Arg Ile Gln Thr Phe Leu Leu Leu Asp Glu Ile Ser Gln Arg Asn Arg 385 390 395 400
- Gln Leu Pro Ser Asp Gly Lys Lys Met Val His Val Gln Asp Phe Thr \$405\$
- Ala Phe Trp Asp Lys Ala Ser Glu Thr Pro Thr Leu Gln Gly Leu Ser 420 425 430
- Phe Thr Val Arg Pro Gly Glu Leu Leu Ala Val Val Gly Pro Val Gly
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- Ala Gly Lys Ser Ser Leu Leu Ser Ala Val Leu Gly Glu Leu Ala Pro 450 455 460
- Ser His Gly Leu Val Ser Val His Gly Arg Ile Ala Tyr Val Ser Gln 465 470 475 480
- Gln Pro Trp Val Phe Ser Gly Thr Leu Arg Ser Asn Ile Leu Phe Gly
  485 490 495
- Lys Lys Tyr Glu Lys Glu Arg Tyr Glu Lys Val Ile Lys Ala Cys Ala 500 505 510
- Leu Lys Lys Asp Leu Gln Leu Leu Glu Asp Gly Asp Leu Thr Val Ile 515 520 525
- Gly Asp Arg Gly Thr Thr Leu Ser Gly Gly Gln Lys Ala Arg Val Asn 530 535 540
- Leu Ala Arg Ala Val Tyr Gln Asp Ala Asp Ile Tyr Leu Leu Asp Asp 545 550 555 560
- Pro Leu Ser Ala Val Asp Ala Glu Val Ser Arg His Leu Phe Glu Leu 565 570 575
- Cys Ile Cys Gln Ile Leu His Glu Lys Ile Thr Ile Leu Val Thr His 580 585 590
- Gln Leu Gln Tyr Leu Lys Ala Ala Ser Gln Ile Leu Ile Leu Lys Asp 595 600 605
- Gly Lys Met Val Gln Lys Gly Thr Tyr Thr Glu Phe Leu Lys Ser Gly 610 615 620
- Ile Asp Phe Gly Ser Leu Leu Lys Lys Asp Asn Glu Glu Ser Glu Gln 625 630 635 640
- Pro Pro Val Pro Gly Thr Pro Thr Leu Arg Asn Arg Thr Phe Ser Glu 645 650 655
- Ser Ser Val Trp Ser Gln Gln Ser Ser Arg Pro Ser Leu Lys Asp Gly 660 665 670
- Ala Leu Glu Ser Gln Asp Thr Glu Asn Val Pro Val Thr Leu Ser Glu 675 680 685
- Glu Asn Arg Ser Glu Gly Lys Val Gly Phe Gln Ala Tyr Lys Asn Tyr 690 695 700
- Phe Arg Ala Gly Ala His Trp Ile Val Phe Ile Phe Leu Ile Leu Leu 705 710 715 720

- Asn Thr Ala Ala Gln Val Ala Tyr Val Leu Gln Asp Trp Trp Leu Ser 725 730 735
- Tyr Trp Ala Asn Lys Gln Ser Met Leu Asn Val Thr Val Asn Gly Gly 740 745 750
- Gly Asn Val Thr Glu Lys Leu Asp Leu Asn Trp Tyr Leu Gly Ile Tyr
  755 760 765
- Ser Gly Leu Thr Val Ala Thr Val Leu Phe Gly Ile Ala Arg Ser Leu 770 780
- Leu Val Phe Tyr Val Leu Val Asn Ser Ser Gln Thr Leu His Asn Lys 785 790 795 800
- Met Phe Glu Ser Ile Leu Lys Ala Pro Val Leu Phe Phe Asp Arg Asn 805 810 815
- Pro Ile Gly Arg Ile Leu Asn Arg Phe Ser Lys Asp Ile Gly His Leu 820 825 830
- Asp Asp Leu Leu Pro Leu Thr Phe Leu Asp Phe Ile Gln Thr Leu Leu 835 840 845
- Gln Val Val Gly Val Val Ser Val Ala Val Ala Val Ile Pro Trp Ile 850 855 860
- Ala Ile Pro Leu Val Pro Leu Gly Ile Ile Phe Ile Phe Leu Arg Arg 865 870 875 880
- Tyr Phe Leu Glu Thr Ser Arg Asp Val Lys Arg Leu Glu Ser Thr Thr 885 890 895
- Arg Ser Pro Val Phe Ser His Leu Ser Ser Ser Leu Gln Gly Leu Trp 900 905 910
- Thr Ile Arg Ala Tyr Lys Ala Glu Glu Arg Cys Gln Glu Leu Phe Asp 915 920 925
- Ala His Gln Asp Leu His Ser Glu Ala Trp Phe Leu Phe Leu Thr Thr 930 935 940
- Ser Arg Trp Phe Ala Val Arg Leu Asp Ala Ile Cys Ala Met Phe Val 945 950 955 960
- Ile Ile Val Ala Phe Gly Ser Leu Ile Leu Ala Lys Thr Leu Asp Ala 965 970 975
- Gly Gln Val Gly Leu Ala Leu Ser Tyr Ala Leu Thr Leu Met Gly Met 980 985 990

- Phe Gln Trp Cys Val Arg Gln Ser Ala Glu Val Glu Asn Met Met Ile 995 1000 1005
- Ser Val Glu Arg Val Ile Glu Tyr Thr Asp Leu Glu Lys Glu Ala Pro 1010 1015 1020
- Trp Glu Tyr Gln Lys Arg Pro Pro Pro Ala Trp Pro His Glu Gly Val 1025 1030 1035 1040
- Ile Ile Phe Asp Asn Val Asn Phe Met Tyr Ser Pro Gly Gly Pro Leu 1045 1050 1055
- Val Leu Lys His Leu Thr Ala Leu Ile Lys Ser Gln Glu Lys Val Gly
  1060 1065 1070
- Ile Val Gly Arg Thr Gly Ala Gly Lys Ser Ser Leu Ile Ser Ala Leu 1075 1080 1085
- Phe Arg Leu Ser Glu Pro Glu Gly Lys Ile Trp Ile Asp Lys Ile Leu 1090 1095 1100
- Thr Thr Glu Ile Gly Leu His Asp Leu Arg Lys Lys Met Ser Ile Ile
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- Pro Gln Glu Pro Val Leu Phe Thr Gly Thr Met Arg Lys Asn Leu Asp 1125 1130 1135
- Pro Phe Asn Glu His Thr Asp Glu Glu Leu Trp Asn Ala Leu Gln Glu
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- Val Gln Leu Lys Glu Thr Ile Glu Asp Leu Pro Gly Lys Met Asp Thr 1155 1160 1165
- Glu Leu Ala Glu Ser Gly Ser Asn Phe Ser Val Gly Gln Arg Gln Leu 1170 1175 1180
- Val Cys Leu Ala Arg Ala Ile Leu Arg Lys Asn Gln Ile Leu Ile Ile 1185 1190 1195 1200
- Asp Glu Ala Thr Ala Asn Val Asp Pro Arg Thr Asp Glu Leu Ile Gln
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- Gln Lys Pro Ser Leu Thr Arg Ala Ile Ile Lys Cys Tyr Trp Lys Ser 35 40 45
- Tyr Leu Val Leu Gly Ile Phe Thr Leu Ile Glu Glu Ser Ala Lys Val 50 55 60
- Ile Gln Pro Ile Phe Leu Gly Lys Ile Ile Asn Tyr Phe Glu Asn Tyr 65 70 75 80
- Asp Pro Met Asp Ser Val Ala Leu Asn Thr Ala Tyr Ala Thr 85 90 95
- Val Leu Thr Phe Cys Thr Leu Ile Leu Ala Ile Leu His His Leu Tyr
  100 105 110
- Phe Tyr His Val Gln Cys Ala Gly Met Arg Leu Arg Val Ala Met Cys 115 120 125
- His Met Ile Tyr Arg Lys Ala Leu Arg Leu Ser Asn Met Ala Met Gly 130 135 140
- Lys Thr Thr Gly Gln Ile Val Asn Leu Leu Ser Asn Asp Val Asn 145 150 155 160
- Lys Phe Asp Gln Val Thr Val Phe Leu His Phe Leu Trp Ala Gly Pro \$165\$ \$170\$ \$175\$
- Leu Gln Ala Ile Ala Val Thr Ala Leu Leu Trp Met Glu Ile Gly Ile 180 185 190
- Ser Cys Leu Ala Gly Met Ala Val Leu Ile Ile Leu Leu Pro Leu Gln 195 200 205
- Ser Cys Phe Gly Lys Leu Phe Ser Ser Leu Arg Ser Lys Thr Ala Thr 210 215 220
- Phe Thr Asp Ala Arg Ile Arg Thr Met Asn Glu Val Ile Thr Gly Ile 225 230 235 240
- Arg Ile Ile Lys Met Tyr Ala Trp Glu Lys Ser Phe Ser Asn Leu Ile 245 250 255
- Thr Asn Leu Arg Lys Lys Glu Ile Ser Lys Ile Leu Arg Ser Ser Cys 260 265 270

- Leu Arg Gly Met Asn Leu Ala Ser Phe Phe Ser Ala Ser Lys Ile Ile 275 280 285
- Val Phe Val Thr Phe Thr Thr Tyr Val Leu Leu Gly Ser Val Ile Thr 290 295 300
- Ala Ser Arg Val Phe Val Ala Val Thr Leu Tyr Gly Ala Val Arg Leu 305 310 315 320
- Thr Val Thr Leu Phe Phe Pro Ser Ala Ile Glu Arg Val Ser Glu Ala 325 330 335
- Ile Val Ser Ile Arg Arg Ile Gln Thr Phe Leu Leu Leu Asp Glu Ile 340 345 350
- Ser Gln Arg Asn Arg Gln Leu Pro Ser Asp Gly Lys Lys Met Val His 355 360 365
- Val Gln Asp Phe Thr Ala Phe Trp Asp Lys Ala Ser Glu Thr Pro Thr 370 375 380
- Leu Gln Gly Leu Ser Phe Thr Val Arg Pro Gly Glu Leu Leu Ala Val 385 390 395 400
- Val Gly Pro Val Gly Ala Gly Lys Ser Ser Leu Leu Ser Ala Val Leu
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- Gly Glu Leu Ala Pro Ser His Gly Leu Val Ser Val His Gly Arg Ile 420 425 430
- Ala Tyr Val Ser Gln Gln Pro Trp Val Phe Ser Gly Thr Leu Arg Ser 435  $\phantom{\bigg|}440\phantom{\bigg|}445\phantom{\bigg|}$
- Asn Ile Leu Phe Gly Lys Lys Tyr Glu Lys Glu Arg Tyr Glu Lys Val 450 455 460
- Ile Lys Ala Cys Ala Leu Lys Lys Asp Leu Gln Leu Leu Glu Asp Gly 465 470 475 480
- Asp Leu Thr Val Ile Gly Asp Arg Gly Thr Thr Leu Ser Gly Gly Gln 485 490 495
- Lys Ala Arg Val Asn Leu Ala Arg Ala Val Tyr Gln Asp Ala Asp Ile 500 505 510
- Tyr Leu Leu Asp Asp Pro Leu Ser Ala Val Asp Ala Glu Val Ser Arg 515 520 525
- His Leu Phe Glu Leu Cys Ile Cys Gln Ile Leu His Glu Lys Ile Thr 530 535 540

- Ile Leu Val Thr His Gln Leu Gln Tyr Leu Lys Ala Ala Ser Gln Ile 545 550 555 560
- Leu Ile Leu Lys Asp Gly Lys Met Val Gln Lys Gly Thr Tyr Thr Glu
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- Phe Leu Lys Ser Gly Ile Asp Phe Gly Ser Leu Leu Lys Lys Asp Asn 580 585 590
- Glu Glu Ser Glu Gln Pro Pro Val Pro Gly Thr Pro Thr Leu Arg Asn 595 600 605
- Arg Thr Phe Ser Glu Ser Ser Val Trp Ser Gln Gln Ser Ser Arg Pro 610 620
- Ser Leu Lys Asp Gly Ala Leu Glu Ser Gln Asp Thr Glu Asn Val Pro 625 630 635 640
- Val Thr Leu Ser Glu Glu Asn Arg Ser Glu Gly Lys Val Gly Phe Gln 645 650 655
- Ala Tyr Lys Asn Tyr Phe Arg Ala Gly Ala His Trp Ile Val Phe Ile 660 665 670
- Phe Leu Ile Leu Leu Asn Thr Ala Ala Gln Val Ala Tyr Val Leu Gln 675 680 685
- Asp Trp Trp Leu Ser Tyr Trp Ala Asn Lys Gln Ser Met Leu Asn Val 690 695 700
- Thr Val Asn Gly Gly Gly Asn Val Thr Glu Lys Leu Asp Leu Asn Trp 705 710 715 720
- Tyr Leu Gly Ile Tyr Ser Gly Leu Thr Val Ala Thr Val Leu Phe Gly
  725 730 735
- Ile Ala Arg Ser Leu Leu Val Phe Tyr Val Leu Val Asn Ser Ser Gln 740 745 750
- Thr Leu His Asn Lys Met Phe Glu Ser Ile Leu Lys Ala Pro Val Leu 755 760 765
- Phe Phe Asp Arg Asn Pro Ile Gly Arg Ile Leu Asn Arg Phe Ser Lys 770 775 780
- Asp Ile Gly His Leu Asp Asp Leu Leu Pro Leu Thr Phe Leu Asp Phe 785 790 795 800
- Ile Gln Thr Leu Leu Gln Val Val Gly Val Val Ser Val Ala Val Ala 805 810 815

- Val Ile Pro Trp Ile Ala Ile Pro Leu Val Pro Leu Gly Ile Ile Phe 820 825 830
- Ile Phe Leu Arg Arg Tyr Phe Leu Glu Thr Ser Arg Asp Val Lys Arg 835 840 845
- Leu Glu Ser Thr Thr Arg Ser Pro Val Phe Ser His Leu Ser Ser Ser 850 855 860
- Leu Gln Gly Leu Trp Thr Ile Arg Ala Tyr Lys Ala Glu Glu Arg Cys 865 870 875 880
- Gln Glu Leu Phe Asp Ala His Gln Asp Leu His Ser Glu Ala Trp Phe 885 890 895
- Leu Phe Leu Thr Thr Ser Arg Trp Phe Ala Val Arg Leu Asp Ala Ile 900 905 910
- Cys Ala Met Phe Val Ile Ile Val Ala Phe Gly Ser Leu Ile Leu Ala 915 920 925
- Lys Thr Leu Asp Ala Gly Gln Val Gly Leu Ala Leu Ser Tyr Ala Leu 930 935 940
- Thr Leu Met Gly Met Phe Gln Trp Cys Val Arg Gln Ser Ala Glu Val 945 950 955 960
- Glu Asn Met Met Ile Ser Val Glu Arg Val Ile Glu Tyr Thr Asp Leu 965 970 975
- Glu Lys Glu Ala Pro Trp Glu Tyr Gln Lys Arg Pro Pro Pro Ala Trp 980 985 990
- Pro His Glu Gly Val Ile Ile Phe Asp Asn Val Asn Phe Met Tyr Ser 995 1000 1005
- Pro Gly Gly Pro Leu Val Leu Lys His Leu Thr Ala Leu Ile Lys Ser 1010 1015 1020
- Gln Glu Lys Val Gly Ile Val Gly Arg Thr Gly Ala Gly Lys Ser Ser 1025 1030 1035 1040
- Leu Ile Ser Ala Leu Phe Arg Leu Ser Glu Pro Glu Gly Lys Ile Trp
  1045 1050 1055
- Ile Asp Lys Ile Leu Thr Thr Glu Ile Gly Leu His Asp Leu Arg Lys \$1060\$ \$1065\$ \$1070
- Lys Met Ser Ile Ile Pro Gln Glu Pro Val Leu Phe Thr Gly Thr Met 1075 1080 1085

Arg Lys Asn Leu Asp Pro Phe Asn Glu His Thr Asp Glu Glu Leu Trp 1090 1095 1100

Asn Ala Leu Gln Glu Val Gln Leu Lys Glu Thr Ile Glu Asp Leu Pro 1105 1110 1115 1120

Gly Lys Met Asp Thr Glu Leu Ala Glu Ser Gly Ser Asn Phe Ser Val 1125 1130 1135

Gly Gln Arg Gln Leu Val Cys Leu Ala Arg Ala Ile Leu Arg Lys Asn 1140 1145 1150

Gln Ile Leu Ile Ile Asp Glu Ala Thr Ala Asn Val Asp Pro Arg Thr 1155 1160 1165

Asp Glu Leu Ile Gln Lys Lys Ile Arg Glu Lys Phe Ala His Cys Thr 1170 1180

Val Leu Thr Ile Ala His Arg Leu Asn Thr Ile Ile Asp Ser Asp Lys 1185 1190 1195 1200

Ile Met Val Leu Asp Ser Gly Arg Leu Lys Glu Tyr Asp Glu Pro Tyr 1205 1210 1215

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Cys Arg Met Pro Arg Thr Leu Arg Arg Leu
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tcataccagt ccacggacta ttatgaacca caccacacag gaggaggtga gcactaggca 180
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20

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<213> Homo sapiens
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Phe Leu Thr Phe Ser Phe Leu Ser Met Val Glu Pro Pro Arg Ala Gly
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3.0

Val Leu Asn Ser Gln Ala Thr Asp Ser Tyr Gln Ser Thr Asp Tyr Tyr 35 40 45

Glu Pro His His Thr Gly Gly Glu His
50 55

<210> 554

<211> 59

<212> PRT

<213> Homo sapiens

<400> 554

Leu Gln Lys Asn Lys Leu Arg Ala Ser Thr Asp Ser Thr Leu Trp Ile
5 10 15

Cys Ala Ala Glu Ala Ser Thr Lys Pro Tyr Phe Tyr Thr Cys Leu Val $20 \hspace{1.5cm} 25 \hspace{1.5cm} 30$ 

Met Leu His Gly Gln Gly Leu Ala Leu Leu Ser Pro Thr Asn Leu Pro 35 40 45

Glu Ile Leu Arg Phe Leu Phe Asn Gly Phe Leu
50 55

<210> 555

<211> 71

<212> PRT

<213> Homo sapiens

<400> 555

Leu Gly Arg Phe Ser Leu Ser Cys Lys Ser Gly His Ser Arg Gly Gln 5 10 15

Pro Gln Leu Gly Ala Thr Ala Gln Gly Lys Val His Met Gly Leu Ser 20 25 30

Thr Ala Gln Gly Ser Ile Gln Asp Ile Lys Val Pro His Ser Ile Asp
35 40 45

Leu Val Ala Lys Lys Lys Gln Thr Leu Ile Ser Phe Cys His Pro
50 55 60

Ser Asp Pro Leu Glu Leu Leu

<210> 556

<211> 81

<212> PRT

<213> Homo sapiens

<400> 556

Asn His Pro Glu Gln Gly Ser Ser Thr Pro Arg Pro Gln Thr His Thr 5 10 15

Ser Pro Arg Thr Ile Met Asn His Thr Thr Gln Glu Glu Val Ser Thr
20 25 30

Arg Gln Ala Lys Glu Ala Ser Pro Val Leu Thr Ala Thr Arg His Gly 35 40 45

Ser Tyr Tyr Ser Leu Asn Ser Ala Ser Thr Gln Ile Ser Asp Asn Ile 50 55 60

Arg Asn Ser Leu Glu His Glu Pro Cys Cys Glu Leu Pro Ile Arg Arg 65 70 75 80

Ile

<210> 557

<211> 54

<212> PRT

<213> Homo sapiens

<400> 557

Ser Leu Ser Ala Thr Pro Leu Thr Leu Trp Asn Ser Ser Asp Pro Leu
5 10 15

Glu Gln Ala Tyr Leu Ile Ser Ala Arg Glu Lys Thr Asn Asn Gly Leu 20 25 30

Lys Gly Ser Leu Thr Met Lys Val Ser Ala Asn Ser Trp Leu Arg Cys 35 40 45

Gly Phe His Ile Arg Phe 50

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<212> PRT

<213> Homo sapiens

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<223> Xaa = Any amino acid

<400> 558

Asn Asp Arg Asp Arg Asn Ser Asn Lys Val Ile Xaa Lys Ala Asn Leu  $5 \hspace{1.5cm} 10 \hspace{1.5cm} 15$ 

Ile Tyr Phe Thr Asn Leu Thr Ser Cys Leu Ser Val Gln Asn Gln Thr 20 25 30

Phe Thr Cys Thr Lys Arg His Lys His Leu Gln Cys Ser Ser Val His 35 40 45

Leu Cys Lys Ile Pro Pro Arg Leu Lys Gly Arg Asp Lys Lys Lys 50 55 60

Pro Ser Tyr Leu Ser Gly Val Leu His Ser Arg Ser Tyr 65 70 75

<210> 559

<211> 50

<212> PRT

<213> Homo sapiens

<400> 559

Thr Leu Pro Pro Leu Arg Ser Val Ile Thr Leu Glu Thr His Trp Ser 5 10 15

Thr Asn Pro Val Val Asn Cys Leu Ser Glu Gly Ser Arg Leu Cys Ala 20 25 30

Ser Tyr Glu Asn Leu Met Pro Asp Asp Leu Ser Leu Ser His Phe Ala 35 40 45

Pro Arg

50

<210> 560

<211> 56

<212> PRT <213> Homo sapiens

<400> 560

Ile Gly Ser Leu Lys Gly Pro Thr Thr Ala Gly Ser His Cys Ser Gly

Glu Gly Ser Tyr Gly Thr Phe Tyr Cys Pro Arg Phe Tyr Thr Gly Tyr
20 25 30

Lys Gly Ala Ser Gln Tyr Arg Ser Gly Ser Lys Glu Glu Glu Thr Asn 35 40 45

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Thr Asp Leu Phe Leu Pro Pro Leu
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<223> Xaa = Any amino acid
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Gly Leu Lys Ser Pro Glu Ile Lys Asn Pro Ala Pro Thr Gly Thr Ser
                                  25
                                                      30
Asn Leu Ser Cys Phe Leu Ser Xaa Phe Trp Leu Met Gln Gly Thr Asn
         35
                              40
Ser Leu Pro Arg Glu Asn Tyr Leu Asn
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<210> 562
<211> 59
<212> PRT
<213> Homo sapiens
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<223> Xaa = Any amino acid
<400> 562
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                  5
                                      10
                                                          15
Ala Pro Met His Gly Ile Lys Asn Ser Ile Thr Ser Leu Ile Phe Leu
             20
                                  25
Ile Ser Tyr Leu Xaa Leu Glu Met Ser Ser Leu Ser Glu Ser Leu Val
Leu Ser Ser Gly Asp Tyr Val Leu Asp Thr Pro
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<212> PRT

<213> Homo sapiens

<400> 563

Cys Phe Leu Phe Pro Tyr Leu Trp Leu Tyr Ala Gln Pro Leu Phe Pro
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Lys Gln Gln Pro Pro Ala Leu Ala Pro Gly His Pro Asp Phe Ile His 20 25 30

Thr Gln Asn Glu Gln Ile Asp Pro Ser Pro His Ile Gln Asn Leu Met 35 40 45

Trp Asn Pro His Leu Ser Gln Glu Leu Ala Glu Thr Phe Met Val Arg 50 55 60

Asp Pro Leu Arg Pro Leu Leu Val Phe Ser Leu Ala Asp Ile Arg
65 70 75

<210> 564

<211> 64

<212> PRT

<213> Homo sapiens

<400> 564

Ala Cys Ser Lys Gly Ser Glu Glu Phe Gln Arg Val Arg Gly Val Ala
5 10 15

Glu Arg Asp Gln Cys Leu Phe Leu Leu Cys Tyr Gln Ile Tyr Thr 20 25 30

Val Arg His Leu Tyr Ile Leu Tyr Arg Thr Leu Gly Ser Arg Lys Ser 35 40 45

His Met Asn Leu Pro Leu Ser Ser Gly Ser Gln Leu Trp Leu Ala Pro 50 55 60

<210> 565

<211> 57

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<213> Homo sapiens

<220>

<221> VARIANT

<222> (1)...(57)

<223> Xaa = Any amino acid

<400> 565

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Ala Val Cys Cys Gly Ser Ala Ser Ile Val Ser Leu Leu Glu Gln 20 25 30

Asn Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu 35 40 45

Tyr Ala Val Ser Ser Xaa His Asn Val 50 55

<210> 566

<211> 55

<212> PRT

<213> Homo sapiens

<400> 566

Ile Leu Leu Glu Phe Phe Arg Asn Gln Arg Gly Ser Leu Asn Pro Arg
5 10 15

Lys Thr Val Pro Phe Ile Lys Ser Glu Gly Gly Glu Lys Lys Gly His 20 25 30

Cys Asn His Ser Val Val Ser Ile Asp Ser Ala Ala Ala Leu Leu Pro 35 40 45

Leu Lys Leu Val Leu Leu Pro 50 55

<210> 567

<211> 51

<212> PRT

<213> Homo sapiens

<400> 567

Tyr Ser Asp Phe Asp Val Phe Cys Ser His Thr Tyr Gly Tyr Met Leu
5 10 15

Ser His Cys Ser Gln Ser Ser Ser Pro Leu Leu Trp Pro Leu Gly Ile 20 25 30

Leu Thr Leu Ser Thr His Lys Met Ser Lys Leu Thr Leu Pro Pro Ile
35 40 45

Phe Arg Thr

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<210> 568
<211> 75
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<213> Homo sapiens
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Tyr Val Ala Phe Asn Ser Val Pro Ser Thr Cys Leu Leu Ala Ser Leu
             20
                                 25
                                                     30
Thr Glu Thr Pro Val Thr Thr Ile Leu Thr Ile Ile Ile Asn Leu Thr
         35
                             40
Cys Phe Gln His Ala Glu Ser Ser Tyr Leu Phe Tyr Pro Leu Ala Asp
Phe Leu Leu Gln His Ile Ser Leu Gly Lys Leu
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<210> 569
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<213> Homo sapiens

<400> 574

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Glu Arg Thr Ser Glu Gly Gly Asp Cys His Lys Leu Phe Phe Glu 35 40 45

Thr Arg Val Trp Pro Cys Cys Pro Gly Trp Ser Ala Val Ala 50 55 60

<210> 575

<211> 77

<212> PRT

<213> Homo sapiens

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20 25 30

Ser Leu Glu Pro Gly Arg Leu Arg Glu Glu Asn Arg Leu Asn Pro Gly 35 40 45

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<210> 576

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<400> 576

Met Leu Gly Lys Ser Arg Ala Val Cys Leu Pro Ser Thr Thr Val Thr

5 10 15 Thr Val Cys Tyr Leu Ala Ser Ser Ser Ala Ser Arg Glu Thr Ala Thr 20 25 Arg Gln Ala Pro Gly Asn Trp Lys Met Xaa Ser Lys Cys His Ala Gln 40 Leu Leu Phe Thr Phe Tyr Leu Asn His Phe Tyr Gln Ile Arg Leu Asn Pro Gly Tyr Ser 65 <210> 577 <211> 58 <212> PRT <213> Homo sapiens <400> 577 Met Tyr Leu Glu Asn Ser Phe Tyr Cys Gln Met Ile Leu Leu Lys Arg Cys Arg Leu Ser Lys Ile Ser Thr Gln Arg Val Val Pro Asp Gly Pro 25 Pro Ala Pro Val Pro Gly Ser Phe Pro Met Phe Pro Arg Phe Gly Phe 35 40 Arg Leu Ala Pro Pro Ala Asp Thr Pro 50 55 <210> 578 <211> 52 <212> PRT <213> Homo sapiens <400> 578 Met Gln Leu Ile Tyr Leu Cys Phe Leu Gly Leu Leu Tyr Ile Arg His His Asp Ser Gln Ser Phe Val Ile Leu Tyr Tyr Lys Lys Leu Asn Tyr 25 Tyr Phe Lys Tyr Gly Gln Ile Arg Ala Phe His Ile Ala Lys Val Tyr 35

Gln Pro His 50

<400> 581

<210> 579 <211> 57 <212> PRT <213> Homo sapiens <400> 579 Met His Phe Thr Phe Met Gln Leu Ile Tyr Leu Cys Phe Leu Gly Leu Leu Tyr Ile Arg His His Asp Ser Gln Ser Phe Val Ile Leu Tyr Tyr 25 20 Lys Lys Leu Asn Tyr Tyr Phe Lys Tyr Gly Gln Ile Arg Ala Phe His 40 Ile Ala Lys Val Tyr Gln Pro His <210> 580 <211> 68 <212> PRT <213> Homo sapiens <400> 580 Met Glu Leu Arg Thr Lys Ala Leu Arg Thr Ala Gln Gln Leu Thr Ser 5 Cys Val Thr Ala Leu Lys Ala Ala Gly Pro Pro Leu Thr Phe Trp Lys 25 20 Gly Lys Trp Val Gln Cys Cys Leu Pro Leu Trp Gly Leu Leu Gly Ser His Ala Phe Tyr Ile Tyr Ala Val Asp Ile Phe Met Phe Pro Gly Ser 55 Phe Ile His 65 <210> 581 <211> 78 <212> PRT <213> Homo sapiens

Met Leu Glu Val Lys Phe Glu Val Ser Leu Arg Pro Thr Gly Asn Glu

10

Thr Ala Gly Gln Thr His Gly Thr Gln Asp Lys Gly Ser Lys Asp Ser 20 25 30

Thr Ala Ala Asp Ile Leu Cys Asp Ser Leu Glu Ser Ser Arg Pro Ala 35 40 45

Ala His Ile Leu Glu Gly Lys Met Gly Thr Met Leu Ser Ala Thr Leu 50 55 60

Gly Pro Ser Trp Val Thr Cys Ile Leu His Leu Cys Ser 65 70 75

<210> 582

<211> 52

<212> PRT

<213> Homo sapiens

<400> 582

Met Leu Phe Leu Gln Thr Ile Asp Thr Lys Cys Thr Gly Ile Glu Ile
5 10 15

Asn Arg Asn Trp Ser Lys Val Trp His Thr His Ser His Val Asp Val 20 25 30

Lys Leu Cys Leu Glu Phe Leu Cys Gly Val Trp Phe Gly Leu Gly Phe 35 40 45

Leu Gly Val

<210> 583

<211> 61

<212> PRT

<213> Homo sapiens

<400> 583

Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg
5 10 15

Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro 20 25 30

Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly
35 40 45

Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys
50 55 60

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<210> 584
<211> 77
<212> PRT
<213> Homo sapiens
<400> 584
Met Cys Leu Cys Ile Pro Leu Gly Gly Tyr Gln Glu Leu Cys His Cys
                                      10
Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg
                                  25
Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro
                             40
Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly
     50
Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys
                     70
 65
<210> 585
<211> 51
<212> PRT
<213> Homo sapiens
<400> 585
Met Val Tyr Arg Phe Gly Gln Met Ser Asp Asn Pro Phe Tyr Ile Leu
Ala Ser Leu Gly Ser Ser Ser Cys Arg Asn Gly Leu Ala Ser Lys Trp
             20
                                                      30
Arg Gln Ala Asp Pro Ser Asp Gly Tyr Met Glu Pro Cys Phe Gln Leu
                              40
Leu Phe
     50
<210> 586
<211> 61
<212> PRT
<213> Homo sapiens
<400> 586
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Met Leu Val His Ile Tyr Ser Cys Cys Gly Met Val Tyr Arg Phe Gly

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Gln Met Ser Asp Asn Pro Phe Tyr Ile Leu Ala Ser Leu Gly Ser Ser
                                 25
             20
Ser Cys Arg Asn Gly Leu Ala Ser Lys Trp Arg Gln Ala Asp Pro Ser
                             40
Asp Gly Tyr Met Glu Pro Cys Phe Gln Leu Leu Phe
                         55
<210> 587
<211> 1408
<212> DNA
<213> Homo sapiens
<400> 587
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agcccgcccg gtgaagctcg ctgctttccc tacctcctta agtgactgcc aaacgcccac 120
cggctggaat tgctctggtt atgatgacag agaaaatgat ctcttcctct gtgacaccaa 180
cacctgtaaa tttgatgggg aatgtttaag aattggagac actgtgactt gcgtctgtca 240
gttcaagtgc aacaatgact atgtgcctgt gtgtggctcc aatggggaga gctaccagaa 300
tgagtgttac ctgcgacagg ctgcatgcaa acagcagagt gagatacttg tggtgtcaga 360
aggatcatgt gccacagatg caggatcagg atctggagat ggagtccatg aaggctctgg 420
agaaactagt caaaaggaga catccacctg tgatatttgc cagtttggtg cagaatgtga 480
cgaagatgcc gaggatgtct ggtgtgtgt taatattgac tgttctcaaa ccaacttcaa 540
teceetetge gettetgatg gyaaatetta tgataatgea tgecaaatea aagaageate 600
gtgtcagaaa caggagaaaa ttgaagtcat gtctttgggt cgatgtcaag ataacacaac 660
tacaactact aagtetgaag atgggcatta tgcaagaaca gattatgcag agaatgctaa 720
caaattagaa gaaagtgcca gagaacacca cataccttgt ccggaacatt acaatggctt 780
ctgcatgcat gggaagtgtg agcattctat caatatgcag gagccatctt gcaggtgtga 840
tgctggttat actggacaac actgtgaaaa aaaggactac agtgttctat acgttgttcc 900
cggtcctgta cgatttcagt atgtcttaat cgcagctgtg attggaacaa ttcagattgc 960
tgtcatctgt gtggtggtcc tctgcatcac aaggaaatgc cccagaagca acagaattca 1020
cagacagaag caaaatacag ggcactacag ttcagacaat acaacaagag cgtccacgag 1080
gttaatctaa agggagcatg tttcacagtg gctggactac cgagagcttg gactacacaa 1140
tacagtatta tagacaaaag aataagacaa gagatctaca catgttgcct tgcatttgtg 1200
gtaatctaca ccaatgaaaa catgtactac agctatattt gattatgtat ggatatattt 1260
gaaatagtat acattgtctt gatgtttttt ctgtaatgta aataaactat ttatatcaca 1320
caatawagtt ttttctttcc catgtatttg ttatatataa taaatactca gtgatgagaa 1380
                                                                   1408
aaaaaaaaa aaaaaaaaa rwmgaccc
 <210> 588
 <211> 81
 <212> PRT
 <213> Homo sapiens
 <400> 588
 Met Pro Gln Lys Gln Gln Asn Ser Gln Thr Glu Ala Lys Tyr Arg Ala
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Leu Gln Phe Arg Gln Tyr Asn Lys Ser Val His Glu Val Asn Leu Lys

145

150

20 25 30 Gly Ala Cys Phe Thr Val Ala Gly Leu Pro Arg Ala Trp Thr Thr Gln 35 40 Tyr Ser Ile Ile Asp Lys Arg Ile Arg Gln Glu Ile Tyr Thr Cys Cys Leu Ala Phe Val Val Ile Tyr Thr Asn Glu Asn Met Tyr Tyr Ser Tyr 70 75 Ile <210> 589 <211> 157 <212> PRT <213> Homo sapiens <400> 589 Met Thr Met Cys Leu Cys Val Ala Pro Met Gly Arg Ala Thr Arg Met Ser Val Thr Cys Asp Arg Leu His Ala Asn Ser Arg Val Arg Tyr Leu 25 Trp Cys Gln Lys Asp His Val Pro Gln Met Gln Asp Gln Asp Leu Glu 35 Met Glu Ser Met Lys Ala Leu Glu Lys Leu Val Lys Arg Arg His Pro 55 Pro Val Ile Phe Ala Ser Leu Val Gln Asn Val Thr Lys Met Pro Arg Met Ser Gly Val Cys Val Ile Leu Thr Val Leu Lys Pro Thr Ser Ile 85 90 Pro Ser Ala Leu Leu Met Gly Asn Leu Met Ile Met His Ala Lys Ser 100 110 Lys Lys His Arg Val Arg Asn Arg Lys Leu Lys Ser Cys Leu Trp 115 120 Val Asp Val Lys Ile Thr Gln Leu Gln Leu Leu Ser Leu Lys Met Gly 135 Ile Met Gln Glu Gln Ile Met Gln Arg Met Leu Thr Asn

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<210> 590
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<211> 347

<212> PRT

<213> Homo sapiens

<400> 590

Met Leu Leu Ile Val Ala Arg Pro Val Lys Leu Ala Ala Phe Pro Thr

Ser Leu Ser Asp Cys Gln Thr Pro Thr Gly Trp Asn Cys Ser Gly Tyr
20 25 30

Asp Asp Arg Glu Asn Asp Leu Phe Leu Cys Asp Thr Asn Thr Cys Lys 35 40 45

Phe Asp Gly Glu Cys Leu Arg Ile Gly Asp Thr Val Thr Cys Val Cys 50 55 60

Gln Phe Lys Cys Asn Asn Asp Tyr Val Pro Val Cys Gly Ser Asn Gly 65 70 75 80

Glu Ser Tyr Gln Asn Glu Cys Tyr Leu Arg Gln Ala Ala Cys Lys Gln 85 90 95

Gln Ser Glu Ile Leu Val Val Ser Glu Gly Ser Cys Ala Thr Asp Ala 100 105 110

Gly Ser Gly Ser Gly Asp Gly Val His Glu Gly Ser Gly Glu Thr Ser 115 120 125

Gln Lys Glu Thr Ser Thr Cys Asp Ile Cys Gln Phe Gly Ala Glu Cys 130 135 140

Asp Glu Asp Ala Glu Asp Val Trp Cys Val Cys Asn Ile Asp Cys Ser 145 150 155 160

Gln Thr Asn Phe Asn Pro Leu Cys Ala Ser Asp Gly Lys Ser Tyr Asp 165 170 175

Asn Ala Cys Gln Ile Lys Glu Ala Ser Cys Gln Lys Gln Glu Lys Ile 180 185 190

Glu Val Met Ser Leu Gly Arg Cys Gln Asp Asn Thr Thr Thr Thr Thr 195 200 205

Lys Ser Glu Asp Gly His Tyr Ala Arg Thr Asp Tyr Ala Glu Asn Ala 210 215 220

Asn Lys Leu Glu Glu Ser Ala Arg Glu His His Ile Pro Cys Pro Glu 225 230 235 240

20

His Tyr Asn Gly Phe Cys Met His Gly Lys Cys Glu His Ser Ile Asn 245 250 Met Gln Glu Pro Ser Cys Arg Cys Asp Ala Gly Tyr Thr Gly Gln His 265 270 Cys Glu Lys Lys Asp Tyr Ser Val Leu Tyr Val Val Pro Gly Pro Val 275 280 Arg Phe Gln Tyr Val Leu Ile Ala Ala Val Ile Gly Thr Ile Gln Ile 295 300 Ala Val Ile Cys Val Val Val Leu Cys Ile Thr Arg Lys Cys Pro Arg 315 310 Ser Asn Arg Ile His Arg Gln Lys Gln Asn Thr Gly His Tyr Ser Ser 330 325 335 Asp Asn Thr Thr Arg Ala Ser Thr Arg Leu Ile 340 345 <210> 591 <211> 565 <212> DNA <213> Homo sapien <400> 591 actaaagcaa atgaacaagc tgacttgcta gtatcatctg cattcattga agcacaagaa 60 cttcatgcct tgactcatgt aaatgcaata ggattaaaaa ataaatttga tatcacatgg 120 aaacagacaa aaaatattgt acaacattgc acccagtgtc agattctaca cctggccact 180 caggaagcaa gagttaatcc cagaggtcta tgtcctaatg tgttatggca aatggatgtc 240 atgcacgtac cttcatttgg aaaattgtca tttgtccatg tgacagttga tacttattca 300 catttcatat gggcaacctg ccagacagga gaaagtactt cccatgttaa aagacattta 360 ttatcttgtt ttcctgtcat gggagttcca gaaaaagtta aaacagacaa tgggccaggt 420 tactgtagta aagcatttca aaaattctta aatcagtgga aaattacaca tacaatagga 480 attetetata atteecaagg acaggecata attgaaggaa etaatagaac acteaaaget 540 caattggtta aacaaaaaaa aaaaa 565 <210> 592 <211> 188 <212> PRT <213> Homo sapien <400> 592 Thr Lys Ala Asn Glu Gln Ala Asp Leu Leu Val Ser Ser Ala Phe Ile 10 Glu Ala Gln Glu Leu His Ala Leu Thr His Val Asn Ala Ile Gly Leu

25

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Lys Asn Lys Phe Asp Ile Thr Trp Lys Gln Thr Lys Asn Ile Val Gln
His Cys Thr Gln Cys Gln Ile Leu His Leu Ala Thr Gln Glu Ala Arg
                        55
Val Asn Pro Arg Gly Leu Cys Pro Asn Val Leu Trp Gln Met Asp Val
Met His Val Pro Ser Phe Gly Lys Leu Ser Phe Val His Val Thr Val
                                     90
Asp Thr Tyr Ser His Phe Ile Trp Ala Thr Cys Gln Thr Gly Glu Ser
                                 105
            100
Thr Ser His Val Lys Arg His Leu Leu Ser Cys Phe Pro Val Met Gly
                             120
Val Pro Glu Lys Val Lys Thr Asp Asn Gly Pro Gly Tyr Cys Ser Lys
                        135
                                             140
Ala Phe Gln Lys Phe Leu Asn Gln Trp Lys Ile Thr His Thr Ile Gly
                    150
                                         155
Ile Leu Tyr Asn Ser Gln Gly Gln Ala Ile Ile Glu Gly Thr Asn Arg
                165
                                     170
                                                          175
Thr Leu Lys Ala Gln Leu Val Lys Gln Lys Lys
            180
                                 185
<210> 593
<211> 271
<212> DNA
<213> Homo sapien
<220>
<221> misc_feature
<222> (1) ... (271)
\langle 223 \rangle n = A,T,C or G
<400> 593
actttatgtt cnagtgcana aanceneetg gattgccace ntactetcag ggetgtgant
                                                                         60
tgtgcnccca nagcaacctg ggcacgcggg gacagggggg ccnacaattg agggagcggt
                                                                        120
gtccctagct ggggtctata catgnenggg naagggenge tgagtnecat nagcaaagga
                                                                        180
nctagnatnt gcgggggtgc ggcctgggcc taccctttna agcatccntn gatccactcc
                                                                        240
angaanceng gggtagneag gtttnecaac a
                                                                        271
<210> 594
<211> 376
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(376)
<223> n = A, T, C or G
<400> 594
cctttggggg nggggggaac ctttaccatt gtnccccttt atttcatttg gttngggttc
                                                                         60
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gcgccctcnn gggccaacaa agttatcgtn nttgaagaga anattttttt ggnttngncc

```
180
cgattaagcg ncaaatgtgt agcaaaangc cgtgccactt gtggcgtagc tncgtcgggt
cgattcgacg acaaggcgtn gcgcgntanc gttagtctcn aatngacccn gtggcatgag
                                                                        240
cccacqanqq nttcqtgtcg tcacatggnc tctagacata acgcncnccn ttttttncag
                                                                        300
agggggntgc cgcccttagg gaggnagggg tggggacact agccaancca nantctnacc
                                                                        360
                                                                        376
ccattgaaga aaaggn
<210> 595
<211> 242
<212> DNA
<213> Homo sapien
<220>
<221> misc_feature
<222> (1)...(242)
\langle 223 \rangle n = A,T,C or G
<400> 595
agnotgotgn togtnocotn tatgtggott catnntgagg acaanagtng cactgaggot
                                                                         60
                                                                        120
tgngnatgcc aggcaaggnc aagctggctc aaaaagcatc cacccacctc tgnaangggt
atgccangag cangtgcacc agtcccaact angagncccn ggcatgntac atcttcttcc
                                                                        180
accectnaaa ntttgngcta caangneeat ttttetttt etettaaggg nenentgget
                                                                        240
                                                                        242
<210> 596
<211> 535
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(535)
<223> n = A, T, C or G
<400> 596
accagttgga tactgctaaa nagatattta tgcagcctca tatgttaagt cgtatatttt
                                                                         60
gaaagetttt taaatttttt etttaagaag attttagatg ettateactg agtaecagag
                                                                        120
ggatgtaggc tgatgccctt atcaacaaag tcagggactg tggcacacaa ggattgacta
                                                                        180
                                                                        240
ctgcagacac ggccacaatg ctacctctag agggcctgaa tccccctgcc ctctctggtg
gggagaaggg ctggcagagc cattagcatg ggctccggcc aatcctggcc actttgacac
                                                                        300
teetggtget gacccagggt cetggaggaa gggatgaggt gggcagtaga gatgetcagg
                                                                        360
gcagtggccc ctttccatcc acactggaac tatttcagta ttttaccacc aattcagcca
                                                                        420
ttcccttgtg cgctggctga acatcagccc tgctccaggt ctcagtttcc cctttgtaaa
                                                                        480
gggaaagctc tggattcagg gagtgatgaa gaggtcatca tggtcttgag aattc
                                                                        535
<210> 597
<211> 257
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
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<222> (1)...(257)
<223> n = A, T, C or G
<400> 597
                                                                         60
tttcnatacc caaaantacc ccatattang accanacatt tgtctnggaa aaattaccat
tntntaacnt ttgggccacc tgagannaaa tgggtgtaat ncatgataag atggancagn
                                                                        120
                                                                        180
attnctctta agatnngatn agaccccgtt tttcacggaa catatccaag nacccaatag
gnaacaagcc acgggnggag tcacaaacat atattettta etetcataat cegtnncaca
                                                                        240
                                                                        257
naactnttgn acttgac
<210> 598
<211> 222
<212> DNA
<213> Homo sapien
<220>
<221> misc_feature
<222> (1) ... (222)
<223> n = A, T, C or G
<400> 598
nntqqntacc qtcnaaactt nncttggtac ccgagctcgg atccactagt ccagtgtggt
                                                                         60
ggaattccat tgtgttgggc tataagctgt aatagtggag ncgtgctngg ttcattgcan
                                                                        120
nagnecetee geanneaene ttgnnacaae etgtgagnag genataaatt atteaeataa
                                                                        180
tcatcactgc atgaanctga ctcaaacgca tccacntaca cc
                                                                        222
<210> 599
<211> 238
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(238)
<223> n = A,T,C or G
<400> 599
                                                                         60
qcatqacatc ancgatgtnt ttggnnacct ganattngct aaaactngng natgccgggn
atgnaggttt ggtantgatc tatgcactca catctcatgg ggacgtttca tgtggagtgn
                                                                        120
togacaangt tgctgnancn qaqaagtgat gatctcagtt gaaagggtca tgtgaataca
                                                                        180
cnttacactt gaaaaagaag cacattggga atatcacgaa acgnccacca acatcctg
                                                                        238
<210> 600
<211> 232
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1) ... (232)
<223> n = A,T,C or G
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<400> 600
cgaactattt agactaccta ggaaaattat tttagtatca gaagaatatc aggggtgtag
                                                                         60
tactcatcag agctaaatga gagcgcttta aaaatgttag tttgtcttcc gccatttcta
                                                                        120
cagaaagctg caatttcagg ttttcaacct aataggtgat atttaanaaa aaaaaaaagc
                                                                        180
aatcgcaaat agccccactg cttttacaaa tcatttttc cccaacacaa tg
                                                                        232
<210> 601
<211> 547
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(547)
<223> n = A, T, C \text{ or } G
<400> 601
cattgtgttg gggaaaaaat gatttgtata agcagtgggg ctatttgcga ttgcttttt
                                                                         60
tttttcttaa atatcaccta ttagqttgaa aacctgaaat tgcagctttc tgtagaaatg
                                                                        120
gcggaagaca aactaacatt tttaaagcgc tctcatttag ctctgatgag tactacaccc
                                                                        180
ctnatattct tctgatacta aaataatttt cctagtgtag tctaaacttt tttaaaaaga
                                                                        240
catgtaatcc gcggagttag taactcaaaa cgagtgcatc tnggaagtat cgcagccgtt
                                                                        300
nctggatnaa attcccagct tgctngcttg ctnagccggg gggcggtnaa aaaaacatct
                                                                        360
gcagecengg ggnaaaaace ttegcattgt tettacgtgt ttacgttatt ttattteect
                                                                        420
nnagcaaqqc ngqqanttgg ggactcgaaa tggtacaqtt gggctgggga tcqcccttgt
                                                                        480
tacataaaag ncgtccagaa gagggacggt tacaggcngg ganctccaaa ggtcagtccc
                                                                        540
tgccatt
                                                                        547
<210> 602
<211> 826
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(826)
<223> n = A, T, C \text{ or } G
<400> 602
cggggggnnt tacgtctctc tggacgcttt tattgtacca gggcgatccc agcccaactg
                                                                         60
taccattcga gtccctactc ctgccttgct ctagggaaat aaaataacgt aaacacgtaa
                                                                        120
gaacaatgcg aaagcgtttt cttccctagg ctgcagattg tcttcttcac cgcccctgct
                                                                        180
tagctagcta gctagctggg aatttaatcc agaaacggct tgcgatacct cctagatgca
                                                                        240
ctcgttttga gttacaaact ccgcggatta catgtctttt taaaaaagtt tagactacac
                                                                        300
tagggaaaat tattttagta tcagaagaat atcagggggt gtagtactca tcagagctna
                                                                        360
atgagagege tttaaaaaatg ttagtttgte tteegeeatt tetacagaaa getgeaattt
                                                                        420
caggttttca ncctaatagg tgatatntaa gaaaaaaaaa acaatcgcan atagcccact
                                                                        480
gcttttacaa atcatttttc tcttctaggt atagcctgtc aggtggccta atgtattttt
                                                                        540
gacateteta ggaattttaa tagaccagaa atgggtgeca gagatatgee tgeactaate
                                                                        600
ttaagtgggg atttatgtat ttctcaanca agtgattaaa gcaaaactag gcacgaatga
                                                                        660
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aatcaagatc tttaggccag	aaatcatgaa	nanttttana	attattttan	gaatctgtgg	720
cttctcttct taaaatngaa	aaaaaattg	tttaaaccca	naaggtctga	atacccaagc	780
nccctgaacn anagaacaan	gccggagcac	cccctcccaa	atcccc		826
210 622					
<210> 603					
<211> 817					
<212> DNA					
<213> Homo sapien					
<220>					
<221> misc feature					
<222> (1) (817)					
$\langle 223 \rangle$ n = A,T,C or G					
(223)  11 = 11, 176 61 6					
<400> 603					
nnangacttt tgtggtntta	tacaattntt	ttttctattt	ctatgaagag	aaagccacag	60
agtcctaaaa taattctaaa					120
tcgtgcctag ttttgcttta	atcacttgct	tgagaaatac	ataaatcccc	acttaagatt	180
agtgcaggca tatctctggc	acccatttct	ggttctatta	aaattcctag	agatgtcaaa	240
aattacatta ggccacctga	caggctatac	ctagaagaga	aaaaatgatt	tgtaaaagca	300
gtggggctat ttgcgattgc	tttttttt	tcttaaatat	cacctattag	gttgaaaacc	360
tgaaattgca gctttctgta	gaaatggcgg	aagacaaact	aacattttta	aagcgctctc	420
atttagctct gatgagtact	acacccctga	tattcttctg	atactaaaat	aattttccta	480
gtgtagtcta aacttttta					540
tgcatctagg aggtatcgca	agccgtttct	ggattaaatt	cccagctagc	ttgcttgctt	600
agcaggggcg ggnaaanaag					660
tacgtgttta cgttatttta	tttcctanaa	caaggcngaa	ttgggactcg	aatggttcag	720
ttggggtggg ggatcccctg	gtncataaaa	ngtcanaaag	anggtacagg	cggaacncca	780
agggtegtee tgeatttana	ctcggaattt	tggtgcc			817
<210> 604					
<211> 694					
<212> DNA					
<213> Homo sapien					
-					
<220>					
<221> misc_feature					
<222> (1)(694)					
$\langle 223 \rangle$ n = A,T,C or G					
<400> 604		<b></b>		L	<b>C</b> 0
cttttcaaat catttttnct		_		_	60 120
gacateteta ngaattttaa	-			•	180
cttaagtggg gatttatgta aaatcaagat ¢ttttaggca	_		_		240
tqqctttctc ttcatagaaa	_		<del>-</del>		300
agccaaagca acactganca	_	_			360
aattatacta ccagggtgta	=				420
agaccaatgg ancagaataa	_	-		-	480
ttatcaataa cnaacaccaa	_				540
ggnaaaaact gggaaatcca	=				600
	55	- 5	5		- * *

```
acgcaaannt caacttcgga atgggattac aaaacttaag acattccaac ccaagaaact
                                                                        660
atnaaancta ctattaagaa aacagatcnc nccc
                                                                        694
<210> 605
<211> 678
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(678)
<223> n = A, T, C or G
<400> 605
taaaaatcta qactacacta ggaaattatt ttantatcag aagaatatca ggggtgtagt
                                                                         60
actcatcana gctaaatgag agcgctttaa aaatgttagt ttgtcttccg ccatttctac
                                                                        120
agaaagctgc aatttcaggt tttcaaccta ataggtgata tttaagaaaa aaaaaaagca
                                                                        180
atogcaaata gececaetge tittacaaat cattititet etictaggia tageetgica
                                                                        240
ggtggcctaa tgtaattttt gacatctcta ggaattttaa tagaaccaga aatgggtgcc
                                                                        300
aqaqatatgc ctgcactaat cttaagtggg gatttatgta tttctcaagc aagtgattaa
                                                                        360
agcaaaacta ggcacgattg aaatcaanat cttttaggca agaaagtcat gatgagtttt
                                                                        420
anaattattt taggactctg tggctttctc ttcatagaaa tagaaaaaaa aaattgtata
                                                                        480
aaaaccacaa aaggtcctga atagcccaaa gcaacactga acaaaangaa caaagcagga
                                                                        540
agcaacac taccggaatt caattatact accaaggtgt antaaccaaa acagcattct
                                                                        600
attgggcata aaatagacca aagaccagtg ggaaacagaa taaagaancc caaaataaat
                                                                        660
cctatattta engecene
                                                                        678
<210> 606
<211> 263
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(263)
<223> n = A, T, C or G
<400> 606
gtggggteng cancageeaa eteagettee tttegggett tgttageaga eggateatee
                                                                        60
tetaftecae fgtgnteaaa tteeattgtg tgggggeene tegeetegge canagatetg
                                                                        120
agtgancana entgtececa etgaggtgee ceacagengn ttgtntteag cangggetna
                                                                        180
caactegace ggeagegnan ggetggeaga antgngegee tnneteatte etaegengtn
                                                                        240
ngccgcagga aggangacag gcc
                                                                        263
<210> 607
<211> 22
<212 DNA
<213 Artificial Sequence
<220>
<223 Primer
```

```
<400> 607
                                                                         22
ccatgtgggt cccggttgtc tt
<210> 608
<211> 22
<212> DNA
<213> Artificial Sequence
<220>
<223> Primer
<400> 608
                                                                         22
gataggggtg ctcaggggtt gg
<210> 609
<211> 40
<212> DNA
<213> Artificial Sequence
<220>
<223> Primer
<40þ> 609
gctggacagg gggcaaaagc tggggcagtg aaccatgtgc
                                                                         40
<210> 610
<211> 27
<212> DNA
<213> Artificial Sequence
<220>
<223> Primer
<400> 610
ccttgtccag atagcccagt agctgac
                                                                         27
<210> 611
<211> 46
<212> DNA
<213> Artificial Sequence
<220>
<223> Primer
<400> 611
gatagagaaa accgtccagg ccagtattgt gggaggctgg gagtgc
                                                                         46
<210> 612
<211> 40
<212> DNA
```

```
<213> Artificial Sequence
<220>
<223> Primer
<400> 612
gcacatggtt cactgcccca gcttttgccc cctgtccagc
                                                                         40
<210> 613
<211> 38
<212> DNA
<213> Artificial Sequence
<220>
<223> Primer
<400> 613
                                                                         38
gccgctcgag ttagaattcg gggttggcca cgatggtg
<210> 614
<211> 53
<212> DNA
<213> Artificial Sequence
<220>
<223> Primer
<400> 614
cggcgggcat atgcatcacc atcaccatca catcataaac ggcgaggact gca
                                                                         53
<210> 615
<211> 46
<212> DNA
<213> Artificial Sequence
<220>
<223> Primer
<400> 615
gcactcccag cctcccacaa tactggcctg gacggttttc tctatc
                                                                         46
<210> 616
<211> 1350
<212> DNA
<213> Homo sapien
<400> 616
atdcatcacc atcaccatca catcataaac ggcgaggact gcagcccgca ctcgcagccc
                                                                         60
tgdcaggcgg cactggtcat ggaaaacgaa ttgttctgct cgggcgtcct ggtgcatccg
                                                                        120
cagtgggtgc tgtcagccgc acactgtttc cagaactcct acaccategg gctgggcctg
                                                                        180
cadagtettg aggeegacea agageeaggg ageeagatgg tggaggeeag ceteteegta
                                                                        240
```

```
cggcacccag agtacaacag accettgete getaacgace teatgeteat caagttggac
                                                                       300
gaatccgtgt ccgagtctga caccatccgg agcatcagca ttgcttcgca gtgccctacc
                                                                       360
gcdgggaact cttgcctcgt ttctggctgg ggtctgctgg cgaacggcag aatgcctacc
                                                                       420
gtģctgcagt gcgtgaacgt gtcggtggtg tctgaggagg tctgcagtaa gctctatgac
                                                                       480
ccdctgtacc accccagcat gttctgcgcc ggcggagggc aagaccagaa ggactcctgc
                                                                       540
aa¢ggtgact ctggggggcc cctgatctgc aacgggtact tgcagggcct tgtgtctttc
                                                                       600
ggaaaagccc cgtgtggcca agttggcgtg ccaggtgtct acaccaacct ctgcaaattc
                                                                       660
ac¢gagtgga tagagaaaac cgtccaggcc agtattgtgg gaggctggga gtgcgagaag
                                                                       720
cattcccaac cetggcaggt gettgtggcc tetegtggca gggcagtetg eggeggtgtt
                                                                       780
ctdgtgcacc cccagtgggt cctcacagct gcccactgca tcaggaacaa aagcgtgatc
                                                                       840
ttgctgggtc ggcacagcct gtttcatcct gaagacacag gccaggtatt tcaggtcagc
                                                                       900
cacagettee cacaceeget etacgatatg agesteetga agaategatt ceteaggeea
                                                                       960
ggtgatgaet ceagecaega ceteatgetg etecgeetgt cagageetge egageteaeg
                                                                      1020
gatgctgtga aggtcatgga cctgcccacc caggagccag cactggggac cacctgctac
                                                                      1080
gc¢tcaggct ggggcagcat tgaaccagag gagttcttga ccccaaagaa acttcagtgt
                                                                      1140
gtigacetee atgttattte caatgaegtg tgtgegeaag tteaceetea gaaggtgaee
                                                                      1200
aadttcatgc tgtgtgctgg acgctggaca gggggcaaaa gctggggcag tgaaccatgt
                                                                      1260
gcdctgcccg aaaggccttc cctgtacacc aaggtggtgc attaccggaa gtggatcaag
                                                                      1320
gadaccatcg tggccaaccc cgaattctaa
                                                                      1350
<210> 617
<211> -449
```

```
<212> PRT
<213> Homo sapien
<400> 617
Met His His His His His Ile Ile Asn Gly Glu Asp Cys Ser Pro
 1
                                    10
His Ser Gln Pro Trp Gln Ala Ala Leu Val Met Glu Asn Glu Leu Phe
                                25
Cys Ser Gly Val Leu Val His Pro Gln Trp Val Leu Ser Ala Ala His
                            40
Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly Leu His Ser Leu Glu
    50
                        55
Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu Ala Ser Leu Ser Val
65
                    70
                                        75
                                                             80
Arg His Pro Glu Tyr Asn Arg Pro Leu Leu Ala Asn Asp Leu Met Leu
                                    90
Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp Thr Ile Arg Ser Ile
                                105
Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn Ser Cys Leu Val Ser
                            120
Gly Trp Gly Leu Leu Ala Asn Gly Arg Met Pro Thr Val Leu Gln Cys
                        135
Val Asn Val Ser Val Val Ser Glu Glu Val Cys Ser Lys Leu Tyr Asp
                                        155
Pro Leu Tyr His Pro Ser Met Phe Cys Ala Gly Gly Gln Asp Gln
                165
                                    170
Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly Pro Leu Ile Cys Asn Gly
                                185
Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys Ala Pro Cys Gly Gln Val
```

```
200
       195
Gly Val Pro Gly Val Tyr Thr Asn Leu Cys Lys Phe Thr Glu Trp Ile
                        215
                                             220
Glu Lys Thr Val Gln Ala Ser Ile Val Gly Gly Trp Glu Cys Glu Lys
                    230
                                         235
His Ser Gln Pro Trp Gln Val Leu Val Ala Ser Arg Gly Arg Ala Val
                245
                                     250
Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala His
                                265
Cys Ile Arg Asn Lys Ser Val Ile Leu Leu Gly Arg His Ser Leu Phe
                            280
His Pro Glu Asp Thr Gly Gln Val Phe Gln Val Ser His Ser Phe Pro
    290
                        295
His Pro Leu Tyr Asp Met Ser Leu Leu Lys Asn Arg Phe Leu Arg Pro
                    310
                                         315
Gly Asp Asp Ser Ser His Asp Leu Met Leu Leu Arg Leu Ser Glu Pro
                325
                                     330
Ala Glu Leu Thr Asp Ala Val Lys Val Met Asp Leu Pro Thr Gln Glu
                                345
Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser Gly Trp Gly Ser Ile Glu
                            360
                                                 365
Pro Glu Glu Phe Leu Thr Pro Lys Lys Leu Gln Cys Val Asp Leu His
                        375
                                             380
Val Ile Ser Asn Asp Val Cys Ala Gln Val His Pro Gln Lys Val Thr
                    390
                                         395
385
Lys Phe Met Leu Cys Ala Gly Arg Trp Thr Gly Gly Lys Ser Trp Gly
                405
                                     410
Ser Glu Pro Cys Ala Leu Pro Glu Arg Pro Ser Leu Tyr Thr Lys Val
            420
                                 425
Val His Tyr Arg Lys Trp Ile Lys Asp Thr Ile Val Ala Asn Pro Glu
                            440
        435
Phe
<210> 618
<211> 385
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(385)
<223> n = A,T,C \text{ or } G
<400> 618
ctgtgctgag aaccaaaagc tatgancact gcttttccaa atgtccataa naccaacatt
                                                                         60
tttatcacta ccaccatcac ctgggagete nttagaaage tagteteeeg ggeaceaece
                                                                        120
tggcctactg aacctaatgt gcatttaaca agattnacgt ngaaatctgc aaagcacagg
                                                                        180
ggengataac agtaccacct gntctggttc ctanccccan gacccttaca gtctaactgg
                                                                        240
gacacaaggg cttnaaatca aattgcctat cattaagata tacaanganc ntgagaaact
                                                                        300
gctncactta tntattaagg ngctctaaga cttagaaacn aaangcantg ctgagangat
                                                                        360
```

<213> Homo sapien

```
385
tcaaatatga ngggggncac tttnc
<210> 619
<211> 869
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(869)
<223> n = A, T, C \text{ or } G
<400> 619
                                                                         60
gatatecegg gaattegegg cegegtegac etetaettgt ttagacataa atgeagteta
gcattaaaga tcctttaaaa aaatgttttc ccaatggtta aaagacaagc tcaaataaat
                                                                        120
gaacteteat acatatgeca aaattgatga gtagataaat attteagtag gtagttaeta
                                                                        180
gctttctgtg tatgagtaaa catatgggag aaatttaaaa cactaaagta gactcaatga
                                                                        240
aagcatagta tootatgtat togtttttca gaaatgtota atgaaggaag gaaacaatga
                                                                        300
atgaatgeec ttatteetet tagagtgetg ggacatggtt ttgeetgaaa actteatgtg
                                                                        360
aattttatat tttgctacac attacaccca tcttagactt atacgtataa gacataaggc
                                                                        420
atatcttatg tcttacatgt ataataatct aagcagaaca aaaaataacg aaatattttc
                                                                        480
ttccccaaat ttttgagaca gatggatttt ccggaaagat gtgtttagct tttaatcctg
                                                                        540
tggttttgtg taccacctgg cacactagag tgttgctcta attcagtgag ttgtaactct
                                                                        600
gggtgaacag tggaaatact agggtacatt ttaaaaatgc taatgctcgg gcctcgctga
                                                                        660
agaccaaatt aattggaatc tctgngggng gnattgatct ttttataatc tttctanang
                                                                        720
                                                                        780
attetaatgg gettecaggg atgaaaacen etgntggage tnggaacett cetttagttt
qqaqaaaccc cgatgagggt ntnttaggcn ccgcctnttt ttggcctggg cttcccccct
                                                                        840
tatnntnttt tggaanggnc cnaattttt
                                                                        869
<210> 620
<211> 339
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(339)
<223> n = A, T, C or G
<400> 620
gngegggeet encegtgett getetegetg eegacgetet tttteeacea getgtaggan
                                                                         60
aagcccgaag accactggtc ccccgggtag cccaagtacc actggtcctc ctggctcctg
                                                                        120
acgctneggg tetteetegt ggegtagaet geeagetteg gagacceete agecceteee
                                                                        180
eqettttete caececagga ggccatcagt agegagetae tgccteggee acaacetece
                                                                        240
agcangatag cccgcggttt ccaatctgcg aaaggaggac cgccnagccc gaaatgccna
                                                                        300
gcccagcnat cactgccacg ccgagccnag cgctcgtgc
                                                                        339
<210> 621
<211> 267
<212> DNA
```

```
<220>
<221> misc feature
<222> (1) ... (267)
\langle 223 \rangle n = A,T,C or G
<400> 621
ggggngcatg gtcccnggta gccaagtaca tggtcctcct ggctcctgac gctacgggtc
                                                                         60
ttcctcqtqq cgtagactqc cagcttcgga gacccctcag ccctccccg cttttctcca
                                                                        120
ccccaggagg ccatcagtag cgagctactg cctcggccac aacctcccag caggatngcc
                                                                        180
cqcqqtttcc aatctgcgaa aggaggaccg ccnagccaga aatgccnagc cnagcgatca
                                                                        240
ctgccacgcc nagccnagcg ctcgtgc
                                                                        267
<210> 622
<211> 847
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(847)
<223> n = A,T,C or G
<400> 622
cttangntgt cgactgacgt catgcatgan ttaaagcaga ggtttggtga aatttatgaa
                                                                         60
                                                                        120
aaatacaaaa ttccggcttg tcctgaggaa gagccactac ttgataactc tacaagagga
acagatgtga aggatattcc ctttaatttg acaaataaca tacctggttg tgaggaagaa
                                                                        180
gatgcatctg aaatatctgt ctcagtggta ttcgagacat ttcctgaaca aaaagaaccc
                                                                        240
agtotoaaaa atatoatooa tooataotat catoogtaot otgggtooca ggaacatgtt
                                                                        300
tgccagtcat cttctaagct tcatttacat gaaaataaat tagactgcga caatgataac
                                                                        360
aaactaggca ttggacatat ttttagtaca gataacaact ttcataatga tgcaagcact
                                                                        420
aaqaaaqcaa ggaacccaga agtggttacg gttgaaatga aagaagacca agagtttgat
                                                                        480
ttqcaaatqa caaaaaatat gaaccaaaat agtgacagtg gcagtacaaa taactataaa
                                                                        540
agectgaaac ctaaattaga aaatetgagt tetttaeeac cagattetga cagaacatea
                                                                        600
ggaagtatat ctacatgaag aattacagca agacatgcca aaagtttaag aatgangtca
                                                                        660
acacattaga aanaagantt ctgggctttg aagaaagaaa atgttccact tcataaagaa
                                                                        720
ggttgaaaga agaatgggag agcccngaan tttttgcccn gaaattttcg ggaaccctac
                                                                        780
tggatgggtc nactggttgg ccatgaatga ataatggact aatcnnccaa ttcctnggga
                                                                        840
                                                                        847
agggaat
<210> 623
<211> 681
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1) ... (681)
<223> n = A,T,C or G
<400> 623
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<212> DNA

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aaaactgtac tcgcgcgctg catgtcgaca ctagtggatc caaagaatcg gcacgagcga
                                                                        60
aaangctcan gcagcccggc tggccgccgc cgctcctccc cccaggaaag ccaangtgga
                                                                       120
ngctgatgtg gctgcangag ctcgtttcac agcccctcan gtgganctgg ttgggccgcg
                                                                       180
gctgccangg gcggaagtgg gtgtccccan gtctcagccc caaggctgcc cctcacaaag
                                                                       240
cactggtggt ttgcctccac tgccaccttg ggctccgaac ccgctcccct gctgtggang
                                                                       300
cccaccgtgg gaatccaggt ccccaggtgg actgcctgcc ttgccctcac tgcccactct
                                                                       360
gcccacactt ccctgcctag anaccgggaa ggggctgtgt cggtantggt gcccacctgg
                                                                       420
atgtggcagc accgactgtg ggggtggacc tggccttgcc gggtgcaaaa gtgggggccc
                                                                       480
ngggaaaagc acctgaagtg gccctgaaaa atccccctt aattttnccc caatttgggg
                                                                       540
ctcnaacaaa aggaaattgc tgaagccaan ggtaccaagg tcacccctaa ggccagggtg
                                                                       600
aaaaqqtccc aaaattccaa tncccaccnt ttgggcttnc ctcttggaac cccggccccc
                                                                       660
                                                                       681
tctcntgaan ttttaaaaaa n
<210> 624
<211> 661
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(661)
<223> n = A,T,C or G
<400> 624
                                                                        60
attggtctta ctgtaccacc gggtggaaat cgatggccgc ggcgtctaaa tatccgattt
tttttttttt tcctcttctg actgtccatg gacaaatgaa actaacttaa tctaactaaa
                                                                       120
                                                                       180
aaacacaact atattttgaa gattttctat ctgcactcaa ggacactttc cacncggttg
                                                                       240
ttgttacctt ttggtcttgt ctctgaacat gaaattnatc tcaagggatt ngatttctgg
acctcctatt cctgctatgg gtttgatatt tcttgggctc cagggccact gttgcattgg
                                                                       300
gntqacagnt acctectage ccataneete ctatettggg aaacaaacet aacaactaeg
                                                                       360
tgtaccttcc atagatctct gattgagtct cagtatnegc ttgctcatgg gcgattcact
                                                                       420
tgaatccgtn attggtgcca acaatcctga ctcatgggnn aatggatcct atcacgttcc
                                                                       480
cctgattngc aacccctgta tacatanatc taatcgcata gaatctagcn tnggntatgc
                                                                       540
geggetaege tateagggnt tgntaactat ngeatggeta egaaneetga teatgatena
                                                                       600
gggtcatgga ctcttatcag gggggttggg ccgngcttct ttttcnnacc ttggtaaaac
                                                                       660
                                                                       661
С
<210> 625
<211> 181
<212> DNA
<213> Homo sapien
<400> 625
gcaacaatca gatcatgtta aagtaaatct ccattgccct ggatcacttc aggatttaat
                                                                        60
tgtccaagga gagcagggtt ctcctgtgaa aaaaaggtgg ggaaatgttt gagagtaaaa
                                                                       120
aatacaaaat tcaaccggtc gaaaatacac cactccattc agtgctctac ccccataagc
                                                                       180
                                                                       181
<210> 626
<211> 181
```

```
<213> Homo sapien
<400> 626
gcaacaatca gatcatgtta aagtaaatct ccattgccct ggatcacttc aggatttaat
                                                                        60
tgtccaagga gagcagggtt ctcctgtgaa aaaaaggtgg ggaaatgttt gagagtaaaa
                                                                        120
aatacaaaat tcaaccggtc gaaaatacac cactccattc agtgctctac ccccataagc
                                                                        180
                                                                        181
<210> 627
<211> 813
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(813)
<223> n = A, T, C \text{ or } G
<400> 627
                                                                        60
accaaqctqq agctcgcgcg cctgcaggtc gacactagtg gatccaaagt gaacgtgaag
                                                                        120
qtqaqcaqaq qaqaacttqc gatggcaaaq ttaaaaacaa gaggagatga tggtcttggt
                                                                        180
gtggcacagg atgttaaaaa aattctcctg tccttaagga gttactgcta tttgagtaat
gtgccacttc cctacatagc cttctatgca gaaatgctat atttccactt cacaacccag
                                                                        240
aacgtgcatt ttattttaca tttagaggag gaacaaacaa ccagaaggca aaaactggtg
                                                                        300
                                                                        360
cattattttt tgcaattete ttggaaagag ttegttttta acttetgete agacageaca
                                                                        420
caactactgg gaatatattt taatttcaaa tctgatgtgt gacatctggt aactcattta
ttgctaatga agttttcaca ggaagcagca gtcaccagta gctcatctta tttttcagtt
                                                                        480
qqcaaaqtgt tgtttacctt ttattggcct gcatcggtgt ctcttatcac aggatattta
                                                                        540
attagaaaac gcaagtagcc taacatagaa nagaaatgga gtggtagata atagtagata
                                                                        600
gaatggctaa atatttttat tacagtgatg taatatcact gnaatttatg gttaaaaaatt
                                                                        660
                                                                        720
atgtaatact caaaaggaat tctcagactg gcgaaacagc tggncaacag ctntcacagg
                                                                        780
qctttnanct cctnttgagc tttccccctg ntggacttta gtcttccttt tacncccgna
qttnccattn nttaccaatt gtnccgggaa ana
                                                                        813
<210> 628
<211> 646
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(646)
<223> n = A,T,C or G
<400> 628
tttgggnggn ggtgtctcnt ttgggtggac tttttgggtc gtagggcccc aaggccgtta
                                                                         60
atcccgtaat aacggaagac gaagaagagt cagaagagtg cttctataag gatcgggacg
                                                                        120
agactacctt agaggaataa aggaaaaaag cagaggagga agagtggtag aaggagtcag
                                                                        180
aagaaaccca cacgtcgttc tgaacctgga gccttatcaa aaaggtctag ataaacgata
                                                                        240
gcgatctcga tatcgagctc aagaggtagg tttagagact tctcgtcctc gagagcgaaa
                                                                        300
```

tggaagatct cgacgacgat aagaagttaa agtgtagagg gtgcttgagg agcgcgtgga

360

```
420
aggattetge ggagggacce ategaegtag agaettgaag geetaetaag gteeacaaga
agcccggctc tttctccgaa tggtcggagc gtacagtatg cgacgtcgat cggcagacaa
                                                                        480
gctggcggta gactcgaagt gttcgggcga atcgacttat aatagtcgcg cgctagtaac
                                                                        540
gtaggaacac gaagagtagt cgaaagaaaa cgtttagtga gggaaaagat tagggaaaaa
                                                                        600
ggagaggett aataactaag acacttggag cetaggeeaa egegaa
                                                                        646
<210> 629
<211> 617
<212> DNA
<213> Homo sapien
<220>
<221> misc_feature
<222> (1)...(617)
<223> n = A, T, C or G
<400> 629
gcccccnccc ccctcctngg gcttatnggg acagacccac gtagtactct aaatcttctc
                                                                         60
                                                                        120
ctacgccgga caacggaccc tataccaatt cgaatcttgg acactccgac cgccggattc
tetteceett teggettece etttetgteg gtacceetee etagtegtet cetacacett
                                                                        180
                                                                        240
cgtaccgtcg atatatagtc gccgcggact agcctattta ggtgtcctag actcgttatt
                                                                        300
gatccactca ttagtctagt actatgcgtc acgtatctta gttgcctaag agggagatta
aatcctccac aagttccgac gaattcctgg actctcgtac tagcaaactt tcttatgagg
                                                                        360
cttccttgta tatcttctgg atgtttctcg tgtcccggtc ctccgctact actagagetc
                                                                        420
                                                                        480
cttgccctat ctctagaagt agaggactct cgggttcgtt ctccaaatct agcgctagag
                                                                        540
ctategetac cegetegatt cececagegg aatettgaaa cetgaggtag tacacaaace
                                                                        600
ctccncatct tccctcggtt gctccttctt ctcatccccc cttcccgcct tctcgggaan
                                                                        617
gaatctactt tancttc
<210> 630
<211> 644
<212> DNA
<213> Homo sapien
<220>
<221> misc_feature
<222> (1)...(644)
\langle 223 \rangle n = A,T,C or G
<400> 630
cnnteggent gggttttntt etgagnnnee ecceecece ecceeceaaa ettacaecea
                                                                         60
ccaaacactt teegeeeect acctaggaga cattagaagg gtttaggett eggegtatag
                                                                        120
taaagteete taeeteggaa gtagagaatt eggtatttaa atteagggtt agaggetege
                                                                        180
tcgttagatt tatagtttag gtttagaatc ggaaaccttc gatcttcctt agaagggtaa
                                                                        240
taagtgaggc cctaaatccg tctaaccaag gcgttaaggt ccgtacctaa acctagtctt
                                                                        300
                                                                        360
atettetate aggegeacea atataggtag gttetaettt egtataggee ttaaggaata
gtteggtagt tategaagge acteetetet aggetagget ttteteagte ttagtactee
                                                                        420
gggaccgtcg tcgcanaaat atcgatggac ggtaggtatc tccgcgttac gcgtcgggct
                                                                        480
                                                                        540
agggatatag agcgaattat cggcgagagg cggtcgctan gaatcggtat caatatgntg
ttctttaccc tacggatatc ggcagaaaac ataaaacctt ctnaccangg ataagggatt
                                                                        600
atcggacccc taaaataaca gtaacattta gantactagt accc
                                                                        644
```

<220>

```
<210> 631
<211> 526
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1) ... (526)
<223> n = A, T, C or G
<400> 631
conteggett gggttttttt etgageeece eeceeecee eeceeecge
                                                                        60
cccatagccc caccggnccc acccaaattt taacaaaata aatntaccta tcgntcacct
                                                                       120
atcccncqta tcqnqtaggt cggtaccggt accggngatc ncnacgattn ttcgggtcgt
                                                                       180
cncccttaan acggncccgt agccnccgga anaaatacta cgagngactc taatntagca
                                                                       240
anaccegceg tenattanta geateettag tettecaatg negnggattn ngaateettn
                                                                       300
naagttatcg ggtagaacgg gtcccggtcc cccgccctct ttncaattaa cgccgggtac
                                                                       360
aaantcggtt tctaaattcc ncacgaattt ngncggcaac attcncgggn ccttattanc
                                                                       420
cntttccaac cccgatacnc nagctcgatc gggctttanc gaatccgggg tcncccccga
                                                                       480
                                                                       526
ngantccggg tcctttgagt ngctctagga cggttacgac ggagga
<210> 632
<211> 647
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(647)
\langle 223 \rangle n = A,T,C or G
<400> 632
tttqqqnqqc qqqnqctcat ttqggtggac tttttgggtc gtaggaacct ggtatgaggg
                                                                        60
gtgttttgag tttcttcttc gtcgtctctg ggaggttcgg tttcgattga gattcgggtt
                                                                       120
cqtctttatc ttacqagqca ccctgatatt gttgcgcttt ggtttggttg tggagagttt
                                                                       180
tgtcctactc tagcgggtca tgcggatgat atgtagcctg cgtggcctga tagtgatgtt
                                                                       240
gtgagcttga gaggggagtt gtgggtgttg cgggcggagt aggaggggtt ggagcaccgg
                                                                       300
gattgggaga tatagaatca taagtgttag gtataggtcg attgagcgag ttcgtggaat
                                                                       360
tegtgtggtc atcataatta gagtgaggat gggctctata tttcttagag gacgcacggt
                                                                       420
cgtgattcgg ggtttgatgg gtgttcttct tgtgggcacg attagcttgt tcatgatggt
                                                                       480
aaggaccata ctgtttcgaa tgaggattcg tgtcttcgga ttgttgtgga tattgtggnc
                                                                       540
tanactattt agtgtaagcc ggaggtggtt tgccgtggtg gagtatccga nnttcattcg
                                                                       600
ganggtatgc gtgcggagcg gtccttgtag acattccgga aaaatgg
                                                                       647
<210> 633
<211> 630
<212> DNA
<213> Homo sapien
```

```
<221> misc feature
<222> (1) ... (630)
<223> n = A, T, C \text{ or } G
<400> 633
teettegget tgggtttttt tetgaceece cececece eccectegga aggeetetag
                                                                        60
qctcccaccc qtctctctaa tcctcaggaa ccgatccacc caaccaactt actaatgtcc
                                                                        120
tacagtaaac acccgagaat ataaacccac acctaggcct ccaatcctac cagggaagca
                                                                       180
agaaqccqta qtctaqcqta ttacqaaccc qaqataqaqa cqqaqatact taqttttatt
                                                                       240
ctctcggaat aggaaagacg actggggagg gaatataggc tagcgcgggg ataggggcta
                                                                       300
tggcggatat gggggcgggt cgctctctta ttcttctata ccacgtcaat aggaatgtag
                                                                       360
atatacctaq atgttcccgt agaaagagac gttagaggtc tccgaagcta taaaggagag
                                                                       420
gcgcgaagaa acttcgtact ctagctttat ataggtagtc gctctagtcc cataagcgac
                                                                        480
gagagateta etagattteg gtategeegt egtatgtatt egaaatagte ttetteeeet
                                                                        540
tttcgatctc ctctctatac tacatggnga ttatagtcnt aagatagtca ggatattagg
                                                                       600
atattagtta tatgacgttc gacgggacgg
                                                                        630
<210> 634
<211> 647
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(647)
<223> n = A,T,C or G
<400> 634
centeggett gggttttttt etgaceeece ceceeece ectecaetaa ganettaace
                                                                        60
caaccctata gtttactcgt ataggggaat cgaggagaaa taggaacgaa gagcgggtga
                                                                        120
taaagagaaa gtactttcct ttatatgtta agagettage gtaatgactt tegttatatg
                                                                        180
qctaqttqat tttatccggc gttatagggc ttagttctgg ttatctcggg tctaattccc
                                                                        240
ttagtatgct cgggagttta acgaggtcac gggatagcgc gtaccctttc taaggttctt
                                                                        300
qqaaaqctat tcqttattta tcqcgattct cgaggtcgaa aggatcaagg atcttccctt
                                                                        360
ttactaccct agtcgggtta gcggtcggtc aaaactagtg tagtaccttt acctcctcga
                                                                        420
aagttatagt cgaaacaacg tattagtcga aattatagcg gatagatcga gacggttctt
                                                                        480
tetegggtte teageeggta atecetetat ttgggggtet tetecetett eccetttgte
                                                                        540
ttccgcctta gcttccaagg ttcctcggaa gcgaggggtt ctacttaagt cgntagcgtt
                                                                        600
ccttataaac cncctacagg cagaccccct tgtaaacggc tcggggt
                                                                        647
<210> 635
<211> 645
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1) ... (645)
<223> n = A,T,C or G
<400> 635
```

```
ccttcggctt gggttttttt ctgagccccc ccccccccc cccgaaactc gccttaccct
                                                                        60
agatacccaa agaatagttc cactcaactt cgtctaagta aaactctaga acttccaaac
                                                                       120
ataaaagact tegegeggtt agetacacag cetaegggaa teteaegaat eeegatteaa
                                                                       180
gtcccactct cgaccacacc ccggtatcgt cgttttccca taccaatgtc gaaaaataaa
                                                                       240
ataaaatcca gtcaagcccc acggtaagcg ggggtagggc taggcgaaga ggcaggaacc
                                                                       300
gttcgaggcc gggggctttc aaaatacaaa acaactactt aaagtttacc ccttctaaag
                                                                       360
tcgggggcaa cggttaaagc acgcctctaa agtactactc gtttcgagaa ggggtagtca
                                                                       420
                                                                       480
tetecegeat agagaetete gegtatatea actegeateg ettetageat teegaeggte
gcccgcggct acatatcttg cggattagct ccgagggact atagggttaa ttagtctagt
                                                                       540
aaattetett agaggatagt eggggtegta gttaggeagt acgaggggac atggnetgeg
                                                                       600
togtgotota cottgacago atactottat aaacatottt ttoot
                                                                       645
<210> 636
<211> 643
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(643)
<223> n = A,T,C or G
<400> 636
                                                                        60
ccttcggctt gggttttttt ctgaccccc ccccccccc cctagcggaa aacaatcccc
accgagattt tattaatcgt aaaactcgcc ttcggtacca agtcttcctc cttcccgtaa
                                                                       120
cetggetece tectagngge tttacgaacg teceteetet tettacgget eggaagtggt
                                                                       180
tacggttaaa tccggaggng gggctaacga atccaaggct aactcctctt anagtttgtt
                                                                       240
gtccncncgt ttagtaagga tccgtggagg gcgagtattt gncccccggc ctttattnta
                                                                       300
                                                                       360
tagttcccta gtacgataaa gntaccggct atcctattac agcggataaa agttatttan
                                                                       420
agggccgacg teneegetag acaggetaca getagnggag gtacegeete egactantee
gttgnttccg acaaggnagt ttcggttaac tccacaaact cctccgccga ctctanggtg
                                                                       480
gggacggcag ttcccncgtt tagtgtgcgt tatagagaag ggcatttgag ttggacgtta
                                                                       540
cnttttaaca taggttattc cgtttaggtt cttgcgggcc cgtgggggta gtncnccggc
                                                                       600
gcgttnntat cggcgatttt ccgcagtttc cgtttccggn tnt
                                                                       643
<210> 637
<211> 631
<212> DNA
<213> Homo sapien
<220>
<221> misc_feature
<222> (1)...(631)
\langle 223 \rangle n = A,T,C or G
<400> 637
                                                                        60
gggttntctc atttgggtgg actttttggg tcgtaggaac cggtatgnag gagtaggagt
cgctgggaag actagaagtt agctacggac gattagtgtg attccactct taataacgag
                                                                       120
taatcgttta cgtcgggttg gtgtttcggg gttttggaga gtaagcgtag ttgtggagtt
                                                                       180
tegeatatag gteecettae tteggegate tegtettetg teggttaggt tattattgtt
                                                                       240
```

catcettege attagtagta gggttggteg gataaatega tagetattet ttagaatteg

300

```
tagtcggaga attcgtgtac gaagtccttt aagttcttta agttcgcgag taagacgtgt
                                                                       360
acggttattt tgtcgtcgac gtaggtgtcg tttacgggag tttcgtttta ggggtttacg
                                                                       420
tagaacgtta ttaagcacgg taatacgata gaggattacg cgacgtattc gtcttagaac
                                                                       480
gtcgattttt cgaaggcgca tttgttatcg aaggggagtc cttggagaat cgagatattc
                                                                       540
caagaatatt acggagatta cagatcggaa ggctcccgag atcggacgta ttaccggtct
                                                                       600
cgcccgaaac gagtaggtat cntccggata a
                                                                       631
<210> 638
<211> 606
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(606)
<223> n = A,T,C or G
<400> 638
                                                                        60
cccccccc ctcaaccatc nattccccac ctcaacgcga attacggttt cgaaagtcga
                                                                       120
caataagtcc ggtcgagtag agggaatcag gggctggtan aaaggaccac gggcggaaaa
                                                                       180
taccggtctc cttccgggga gcgacgtcgg ggaaagggaa gagagcggtc tagttcgtag
                                                                       240
gcaaacaggt cagaaaagtt aaggttaaag gtcggagggg agaggatagc tagtacgctt
agttegggge tegggegeag ggeeaettte etetttegeg tteetttaet etgettaega
                                                                       300
                                                                       360
gttcaggetc cggagttccg cgccggaggt cgtcgcgacg ctaggaatgg ggactcgctc
agtccccggt tatccttcgg gattctatgt tttcgccgat agacggagac cgggtagtag
                                                                       420
                                                                       480
ggttccgtcg taccgccact cgtcgccttg atccggcccg ctccgcttaa gggcgatgaa
agattaggta ttagggctct acgggacgag gcatagggcg ggagaagggg ggaggggtcg
                                                                       540
ggggtcgaag ggantaagaa atcgcantcg cgcggggtcg gtagganccg aaatttttct
                                                                       600
cnncgt
                                                                       606
<210> 639
<211> 592
<212> DNA
<213> Homo sapien
<220>
<221> misc_feature
<222> (1)...(592)
<223> n = A, T, C \text{ or } G
<400> 639
teentegget tgggtttttt tetgageeee ceeceeeee ceecegggaa egagaaaaca
                                                                        60
atcccaccct accgcgggga gtgggttgna cgcttagttc tagaatcctc ggaatcgtcc
                                                                       120
teeggegttg gtagtteegg egatteegag tatgeegaag tgtategete egtetagagg
                                                                       180
ttggtatctg tttatcgcga tgacgctatt gactcggatg ctttcgaagt agggggatag
                                                                       240
gegeatagat aegeeteege ggtgteetet gaagtggeeg cateegtgga egeagegtag
                                                                       300
acagetetgg tggacgataa eggetteteg tacteetaet eeggetatta tgttagagag
                                                                       360
                                                                       420
gacttgtttc tgaacggata taccattagc gaaggggtac cctccgctaa cgcaggcgtt
tetaacagtt etteegggeg eteegaattt agattgaege eteegeagea ttgtgggate
                                                                       480
ctcttccgtt agccctcttt ataggatttc tcctccgccc cgaaagangg ctggtcgtcc
                                                                       540
ccggcangta tgtctagctc gaacgctttg ttactccttt gttttcgaaa na
                                                                       592
```

```
<210> 640
<211> 637
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(637)
<223> n = A, T, C or G
<400> 640
ctttgtggcg gtggntgtct catttgggtg gactttttgg gtcgtaggct tatccgggtn
                                                                         60
gggctcccga agtagcttag gatcgccggc tagttccggt cccgcccgtc gaaagcgcgg
                                                                        120
ttcggcgggc ggccccgcgt tcgttcgcgg gctttaccct catagagtgc caggtctcgg
                                                                        180
ttettaeggg ttegteggeg atagatttta eggegagagg teggtatett egeegettta
                                                                        240
egtteggteg geatetaege etagtteaea ggtagtttat gegeeggage gegtgaegga
                                                                        300
gaggttatac gggacgcgga agaaccgcct ccaaatgact agtacaggct cgttcgggcg
                                                                        360
tagateteet egeteggteg geggttetta ettetaggge egetetaegg tttaaggegg
                                                                        420
tcgttagatc ttagaaacta tactcaagtt tcagtcggaa gaaaggaagt agagagaagg
                                                                        480
gtaaacgatt acctccggtt ctagcccttt ttactcgcat aacgggagaa cqqqqtccqq
                                                                        540
ctctcagata cgcctcgcga gacgtcgcga ttcaacttta acctccgcta gggcatccgt
                                                                        600
atacggttaa cgcggtaaaa gcgacctcgg aaacctc
                                                                        637
<210> 641
<211> 649
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(649)
<223> n = A, T, C \text{ or } G
<400> 641
ctntgtggcg gtggttgtct cagtttgggt ggatttttgg gtcgtaggna acctggtatg
                                                                         60
aggictagit tetteaacga tiettggite agitacqcqa ccctateett atettacaat
                                                                        120
gtcttctaca tcaggttcat caattaatat atcaattaca cattaacgac ggtgtgacgc
                                                                        180
aatatgagaa agtatacatt aaggttatta tatattattc gcttaaaaaag gttcctgaca
                                                                        240
tgggacaact tcacccacca ttctagaagc ccccctcct gtaggacccc ctcgagttcc
                                                                        300
ccattatctt agttcagttt tcatttttta accaggaggg tatcggtttt taataggtac
                                                                        360
tattttgtca aacttttcag aagctttatc ttcaaatata cttgcaccat ctgtactagg
                                                                        420
agcactaact attcgagtct attacagctc aacagaaaat aattgaaatt aaacaaccta
                                                                        480
agtategtee accataacce categggete teaccecatt tetteataag ttetagagea
                                                                        540
tectgagete titectatta ceettgatgg tactcatggt ctaatacece cegeagttat
                                                                       600
aggteettat ggateetatg etaccacegg tetaateeet tetateaen
                                                                       649
<210> 642
<211> 645
<212> DNA
<213> Homo sapien
```

```
<220>
<221> misc_feature
<222> (1)...(645)
<223> n = A, T, C or G
<400> 642
tccttcggct tgggtttttt ttcgtcgcgg gttactatta tcgattgtta cttgtaaagg
                                                                         60
cgatactece accepteace atattagace tectetta quaqequace ecquitagete
                                                                        120
tactcggccg gcgaagacgg cgaacgggta ggaggagcca tatgcaaccc taacqqaqat
                                                                        180
tataagtact gggaaaaata ctagtattaa ggtagcgggt taagataggt ggagagacac
                                                                        240
tattcacgag cataagcact tagaaggtct tctcgaggag aggtaggcta cqqactacqt
                                                                        300
tecttettee tetageeteg agagggagta tagatgatte geaaaagaga ateceteeta
                                                                        360
tacgctggca taactagacg acgcgtcgtc gggaaatctc qccaacccta ttqcqacctc
                                                                        420
caaaaggaag attgtcgttt catagaacgc taatactccg ggtcttcccg aatcatagcc
                                                                        480
gcatatcggt aagaagacgg taaaatcgcg cgattctaac aagattctgt agacttaagg
                                                                        540
ctaagcacta gaagcgatct cgattccgga tcttaagatc atactaatag ttcggtcaca
                                                                        600
ccagacgacg attagccact agaagcccta ctccqtnqaa accqq
                                                                        645
<210> 643
<211> 586
<212> DNA
<213> Homo sapien
<220>
<221> misc_feature
<222> (1)...(586)
<223> n = A,T,C or G
<400> 643
ctttgtggcg gcggtgtctc atttgggtgg atttttgggt cgtaggaacc tggtatgcag
                                                                         60
ggtccgcccg gaattaaaag cgggatcccc aaaacgnngn ttcgcaagaa gagaagaatc
                                                                        120
atagcgatag anctttcata gtacaaaggt aactaagagg aaaataatgc agattcagaa
                                                                        180
ctagttgcca aattagaact cgattaggcc aaggatccga gcctggcgct atcacttcgg
                                                                        240
gacttaagct acggtagagc agtcggtcct gaagcatagc tcccgtagga cgtaggaaac
                                                                        300
tagtccggca cggaggacat actctcgagt ctcggaacgt ctatttaqaa tataaacgca
                                                                        360
ttaacctcag aaggegeega egeggttaet etetagggaa etattteatt eetteeggag
                                                                        420
ctcccctatt tttccaacac atataccggc aaaggaaaat cttntgtcct cggtctaaag
                                                                        480
agagggaaaa aaaacgatat ctaggttcgg gtttatccat ttaaaaanat nqacqcqact
                                                                        540
actccctttc aaagggagtt tccccctagg nagagttcaa cngaag
                                                                        586
<210> 644
<211> 646
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(646)
\langle 223 \rangle n = A,T,C or G
```

```
<400> 644
ctttgtggcg gtggttgtct catttgggtg gcatttttgg gtcgtaggaa cctggtatng
                                                                         60
agggctattt gacttgtttc tcaaatccca tggtatggtg ggtggcgtgc ggggtggcgg
                                                                        120
teggttegge gggggtgggg gtegteetee aaaggagttg etagaggget tttagtggtt
                                                                        180
ttagggcggg aaggggttag agcggagaga cgtcgtcgtg gaagcttctg gcggagcgcg
                                                                        240
agaaggtagt tagcgccggt tcggaagatt ctcagaattc gagaagaggt agtggggcgc
                                                                        300
ggagagagag tttctaagtc taaacgtaga ggtcgtccta gtcgggccgg gagtagcttt
                                                                        360
taagctagag gtcgaggtcc tcgtttaggc tccgggctct tcgggcagta tcctctttct
                                                                        420
cgaggaacgg agcgaccgac gtcgtagccg gacccgtcta tccgtacgtt tagagatacg
                                                                        480
ctcacctcca cgggcgtata tgcccgtata cgtataaacg cgtaatatac tcgcgcgtaa
                                                                        540
aacacgtata cactatatac acgcatcgta cggaccgtat agcgttatac gcgcgcgtat
                                                                        600
attaatttac acttatatac gcgttaacac gatatatcac acnccg
                                                                        646
<210> 645
<211> 654
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(654)
\langle 223 \rangle n = A,T,C or G
<400> 645
ncentegget tgggtttttt tetgacecee ecceecece ecceeggteg acaacqtqce
                                                                         60
caccgttgcc atcccagcat agctggttcg ttctgtttta ttcttagtag tttagttcgc
                                                                        120
ctatagtccc tcgtctatcg tctatcattt aaggaggcgg ggctcgctct ttagggcggg
                                                                        180
tatcttaggt attcttctgg tttcggctgc cgtctcggag tctggtcctt ttgctttcct
                                                                        240
ttcttggtcg aacttcgtgt ttgatcgcgt tgtttctttg gggtcgtcat acctaagggc
                                                                        300
cacttegeca acaaacaagt ttgtgtagte gtttetatta gggttegetg geeggegete
                                                                        360
ttactggttg gcgattttta acgcgtttgg ttttaatttg cttcctcccc tagggctcgc
                                                                        420
teggtettet etetgttege tgetetegte eggeetttgg tgeggggata geteeggeta
                                                                        480
ttancgtgcc gtgtccgtgt ggnttttgtc caatgtgaag gcctaggggt gcgggcttct
                                                                        540
ttggccatgg nttcccctct tgtgancctt aggggtaacg antcgtaatt naaggtcggg
                                                                        600
ggttggnata cgttntangg gangcctgng tccgntattc cttgttttgg cctn
                                                                        654
<210> 646
<211> 645
<212> DNA
<213> Homo sapien
<220>
<221> misc_feature
<222> (1)...(645)
<223> n = A,T,C or G
<400> 646
teettegget tgggtttttt tetgageece eececeece eececaegee aagtacaeag
                                                                        60
acccaccaaa aacaacgtca acacaacttc gggtatacgg accttaagag agaccccgta
                                                                       120
gtagacccta ccacagccat ccaatagtca aacaacaagg gcgcacccaa tccatccata
                                                                       180
gagctatcaa acaacggagg ggaaaggaaa gagcagggtc aacttagcag agatcgaagt
                                                                       240
```

```
eggeactaat teettteaag taetegeteg gettgtagtt eggggtaaag teegetetea
                                                                        300
aagggccaac gaggttttaa agcgaccccc gtatcgagtc ttcttcgtat tcattaaggc
                                                                        360
gttaaaggta cgagacctag aagagagtag aattagccca ccaaatcgcc taaaccggca
                                                                        420
aaaacgacca aaagtcaaag accettacaa atatcacett aaaacgecaa ceecaaaaac
                                                                        480
gcgatcagta acgcacgtac ctttcccacg cttttctttc tttcactctc caaaacaaac
                                                                        540
ccgaatattt agcgcaaaaa atatccgagg gagaattaga agctattacc cgaaaaaaa
                                                                       600
ncgganangg antaaatngt ggggaatana cgtttggttt ttctg
                                                                       645
<210> 647
<211> 753
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(753)
<223> n = A,T,C or G
<400> 647
accttacctg gtaccgggcc cccctcgag ttttttttt tccaaataca actcagattg
                                                                        60
tatacgaaaa gctgataata cattgacttt tgctgtttaa atcccttgag cctttgataa
                                                                       120
tgattttttt tgtgttaaca attgtagtat ataaaatcgg attcaccatc cttctgatgc
                                                                       180
catattgatt agtttgattt tatggtgatg ggatcattgt gtgttaactg tattaagaag
                                                                       240
aaatggattt gattgacttt gcatccattt ttatctgtgt tactttcatg ttttatttaa
                                                                       300
aagcatttct ggaccagaat aagttaagtg gtataatttg ctttttacac gtttatataa
                                                                       360
ttgaagttag caatgtggca aaatctctaa tggaaataaa atgcttcaga atgatgacat
                                                                       420
aaatctgagc tatttcttgc ctggagaaca agtgttattc ataataattt aatagcttct
                                                                       480
gaggtgtttt gttcatgtga tgaaggctta tccaccttgt atcaattcat gggctctgct
                                                                       540
ttgtttaatg tagtcaggtt gttaatacna gacttaagag tcatcctact gtgataagtg
                                                                       600
gtgagtgaag attacatgtc ttangaaaat tatactggga atatctctga cattaatggg
                                                                       660
tttaaatgtt ttaaggctag gggatgatgc aatgganaan atnetteeaa angtttetgg
                                                                       720
ttgtttatat ttgnggaagn catnaagana ccg
                                                                       753
<210> 648
<211> 383
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(383)
<223> n = A, T, C or G
<400> 648
gatatecegg ggaaatgegg aggeetting gettaegtgt ttaeegegta gggeaaagee
                                                                        60
ttgncaaatt cccggccagc ggagcggcga gggtggggac tcacgggaag ttaaacagcc
                                                                       120
togtoggogt cotogaggot coaaaaccag gototaggog gggacgactg cagoogttat
                                                                       180
ggaggccacc gcggctacgg ccgcggctga ggcctcccca ggtggagcgg tggcctggag
                                                                       240
gggaatettg atectgggee agecacetgt caagaggagg eggagegtea tgeetetgga
                                                                       300
agactggatg aatattetee aggageetga egaaggegaa gaagtetttg eagaggaaat
                                                                       360
tgaatgctgt ctgatgctac aat
                                                                       383
```

```
<210> 649
<211> 349
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(349)
\langle 223 \rangle n = A,T,C or G
<400> 649
cgattgtnta cnagtcttag agtaagctta agntcgntac cgagctcgga tccactagtc
                                                                           60
cagtgtggtg ggaattccat tgtgttgggt cactagtaaa tggatttagc tagacanagg
                                                                          120
anatttaccc tattccattt agcacagtga gganaggcta nacagctagg atgcaataaa
                                                                          180
aaaaatttta atgagaaatg tgtgtggtag attaattcta ttaatctcaa gttatagatt
                                                                          240
aaaaaattta agtaccncat aaatgccatt tgcctttgct aangntacat ttttatgaan
                                                                          300
aangacentg cataennaat ganatactgg actttnggna ettgangga
                                                                          349
<210> 650
<211> 306
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1) ... (306)
\langle 223 \rangle n = A,T,C or G
<400> 650
cattgtgttg ggagcatect tecateaget cecatgagaa attetetgtt gggtttaage
                                                                           60
aatccccaaa tatatcatat tgacatgaat atatcatctc ctcaatqtcc aqcattaqca
                                                                          120
gacaagatga gtgctgaaga tgatataact cctacctctt atgtaggcta gaggtaaagt
                                                                          180
ctggctctgc tgactgtggg gacataccga aaaggaatgt gggttaatat caqanqacct
                                                                          240
ccctgcagat ccganantca gggnctggac tttctgggan aggaagcnna aagttatntc
                                                                          300
tgaacc
                                                                          306
<210> 651
<211> 769
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(769)
\langle 223 \rangle n = A,T,C or G
<400> 651
cattgtgttg ggcagggtca tttctaaggc atgggctgga agcttttatt taaaacttta
                                                                          60
catgictiag aagcactcig gitgitgcia ggcagacaat titacatcic tigctatacc
                                                                         120
agttgcatga agttcatcat gcatattggc tgtggaaaac cttaacagca tcatgtcata
                                                                         180
```

<211> 710

```
aggtttcagt aaggtttaaa tgaaatcatg tattaagcac ttagtatagt gcaccttaaa
                                                                        240
tgttagcttc aaaacaatga caacctaact aatgttgaaa gaagcttgtg tttgtaaatt
                                                                        300
atgtcttatt gaaagatgtc atcaaatcct gttatttcta atcccttaaa qtctctcaat
                                                                        360
qtatttcttt ttgccatatc caatgacagg accttagttt aagccagtgg ttctctcaac
                                                                        420
ttctaatcca gagatacctg ggtgtcccca agaccttttc agagcatcct tgatgtcaaa
                                                                        480
accattttca taataatatt aaaatattat ttgctcattg tactcttatt ctctcccaaa
                                                                        540
tattcagcga gttttccaga agctatataa catgtggtaa catcttatca ctctgacgat
                                                                        600
taatagaata tgngnttttg gattcttgng tttaaaattt tctcactttg gggttctaat
                                                                        660
atggnnacga ttaatagata tggnctccat qaccaqanqq ctttaaaqca ntcaataatt
                                                                        720
tttaagagac taagnactat cctttaaaga tngngaactc catcttaat
                                                                        769
<210> 652
<211> 267
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(267)
\langle 223 \rangle n = A,T,C or G
<400> 652
nnangccett taaccattgn ggcetecaeg enntggegge egetetaeaa etagnggate
                                                                         60
cgcnactcta gnanaangat tggctcttnt gggntgggcc ggncgggctg gggcgttaag
                                                                        120
eggggetggg egegeegn ggttgnacna ggegeegeeg ecencacaen eeeggageae
                                                                        180
cetenttgen geentneece geteaceeg egegegegn teegettttt ceneaceean
                                                                        240
agenetnttt atetntgtet eeteegg
                                                                        267
<210> 653
<211> 501
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(501)
\langle 223 \rangle n = A,T,C or G
<400> 653
ccenttnace cattgetgga etceaeegeg gtggeggeeg etctanaact agtgggatee
                                                                         60
ttnenatgag atgngegang gaggaennat ttgetatnet ggatgggget gantentnta
                                                                        120
getnetetag cancagatgg gttategagg aagatgacte caangggeta nanteetatg
                                                                        180
cncatcctaa aanncanctg ctgtnttcag agtacgcgac acatcatcnc tnatgcattg
                                                                        240
ntgancaaga egggeangtg ettateetea gegangatge eettaacean gagetegaat
                                                                        300
ggacntatca centanaggt acanntneeg caccacaca engettgenn cetgaegetg
                                                                        360
gactggaten ettaggeeae caatneeeeg tttneeaeat neetgggaen etananatae
                                                                        420
tcganggggg gcccggtanc caattcgccc taatactgag ccttgntacg nacgctnact
                                                                        480
nggngtccta ttanaacgtt g
                                                                        501
<210> 654
```

```
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(710)
<223> n = A, T, C \text{ or } G
<400> 654
gcgnctttan cncatgctgg gctccacgcg gtggcggccg ctctacacta gtggatccca
                                                                         60
acactgagtc caccacagna aaactcanca ccaggcagac cccacaactg cagaatccag
                                                                        120
gctgcaattc acagactaat cntctagacc cacctcagta ccagatggta ccacacagct
                                                                        180
caaggnttta ggtttgcgtg gtanactcaa tctctatctt tcaccactgc cagcctgact
                                                                        240
tcagagatcc tgngctctgg acagtcctca gtggcaggca actctcagga gcctcaggnt
                                                                        300
tttggcacat cccagnacca gccagctgcc acaggccctg accttntanc aacactgccc
                                                                        360
atgtattcca gacttctanc ataccacagt gccatgctga ttgcatctat agangctcag
                                                                        420
gtgcncctca aanctgtgcc tgctgcagna ngccccacgt ctctggcatg ccccaatgcc
                                                                        480
atgngtggna acanttgact tctgggcatg ntggaattcc ctaccactga ncctgaccat
                                                                        540
aggnggganc ccatttttt cgagggggg gcccggccc caattccncc ntataqnqaq
                                                                        600
negtanttae gegennetta etnggeengt ngtttaacaa egtenntgan etqqqqaaaa
                                                                        660
cccctggnng cnacccaaat taaacngcnt tgcannacat ccccctttcg
                                                                        710
<210> 655
<211> 202
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(202)
<223> n = A, T, C or G
<400> 655
cccctttncc ctttcanccc ccccgttttg gcngccgccn acacctactn catccaccca
                                                                         60
cantegacea eeegagettt ttteegatee cancatenat gengattttn tetntgentg
                                                                        120
ctgngcctgc acctttgnta ggtcaagcct ggcccatctt cgacaacttc ctcatcacca
                                                                        180
acgatgaggc atactctgac ga
                                                                        202
<210> 656
<211> 308
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(308)
<223> n = A, T, C \text{ or } G
<400> 656
gctgntgaaa gaccacaccg aaaaactctn ctttccgact tccacatgat gatcngcatg
                                                                         60
tggtggtgag agacttatca tgacgacatc gcttccnacc atcgcanccn ctgcccaagc
                                                                        120
```

```
ccattcatgg aggcctgggn anttctgtga ntgacntnga cnctanacnc tnccactgtn
                                                                        180
tgctatccag acttgnttng aatatnttat tggcnaaana canttnegga atgctgtgnt
                                                                        240
tgnncattga angatctgat cactatgaga gggtgaggac nncctgctng ctggcantnt
                                                                        300
ntaacccn
                                                                        308
<210> 657
<211> 696
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(696)
<223> n = A,T,C or G
<400> 657
accntttcca caatnetgnn etcecegegg tggeggeege gtegaceage aaccteaget
                                                                        60
gtgggtcttg ttacagtaat gagttactgt aaggaaagtg tgacatttcg agcaatttga
                                                                        120
tttgtttaaa aactagagca gtttcagggt tttccttgta aatctgtctt atgtgtcttc
                                                                        180
aatgttettt ettgaggagt agagaaagga attgttagga atgatgeata aaccatgget
                                                                        240
tattttatct cgctgccacc cataatcaga gcagattctt gggactatga ccctcatgga
                                                                        300
gacatgacaa ttgtgtgtgt ggtgggtggg agaaaagagc tgggaatttt tagggtctag
                                                                        360
agggtccaat caggactatt ttatggagct ctgctcacca actttaagtg agcaccaggg
                                                                        420
gtgngaaagc gaatcttggg ntcaaaanaa caatggnaag gggtaagttg gtatnctgaa
                                                                        480
ctggccactt cggactctta tttaactggg tattctcant taaggaggcn ngggtggtct
                                                                        540
tggcttgtna aggaaagcct gtgcaatgga atgactttaa aaccccccat taaaaaaaaa
                                                                        600
angntataaa tettgggtet taanaangaa geetgggtte tnttaneeca ttttneecee
                                                                        660
gggaaggnaa atnttcttag gnaanggaag ggaagg
                                                                        696
<210> 658
<211> 698
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(698)
\langle 223 \rangle n = A,T,C or G
<400> 658
ctggactccc cgcggtggcg gccgctctag aactagtgga tccgtgttgg ctcaattctc
                                                                        60
aaggetgttg etgtgeggee tgtteeceae aegtgetget eageteagge aageaeegag
                                                                       120
cttgtgttgt ttcatgctca gcgtggaggc ccctcctcca ggtcgctgct ctgtggggtt
                                                                       180
cccatacact caggetecta ggaggagtec atttagaaag ccagggtttt tetcagagte
                                                                       240
ttagttcctt gtgctgtcat ccatttcaca cgacttgggc cctgctcggg gcaacacagc
                                                                       300
aagagaaaag acagggaaaa taagagaggg accttgcaca cacacgctct ggaccacaga
                                                                       360
gccctgtgcc cagctcctct gtcaatacag gtggaatctc gtgcaggatc gcaggggtct
                                                                       420
gtgatgccac caaagagcag gccgggacag ggttaggaga gaaaggagag ggaagtgggg
                                                                       480
gtttctccta cgcactctta tttgcagagg gaaaggcggg tttgtattgg ggttgtcggt
                                                                       540
etttgcaccc acngcacagt tgtgagacac ccccatcctn agatcaaagc cccacataca
                                                                       600
gcttggggaa aaacaaaacn aaacaaaaca aaaacagtaa acctccatgc canttgttgg
                                                                       660
```

```
gnaagttttn aatttncttc cccnacccan cttgcttc
                                                                        698
<210> 659
<211> 750
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(750)
<223> n = A, T, C \text{ or } G
<400> 659
ncaanctggn ctccaccgcg gtggcggccg ctctagacta gtggatcctc ctcatgggcc
                                                                         60
tggatatete tgaacatatg atgaacattg ettatgaaaa attatttgta ngaaaattgt
                                                                        120
gaggcctaag aatgntattt tettttagtg atggtetttg tttgettetg taaggnaett
                                                                        180
gtgggcactc gtaagcttgg atctctttaa tctaatacca gntttgagat tttcttggcc
                                                                        240
ccatagatga attaaaactg gcgtacttct tgtttacaag anggataagt ctcctagggt
                                                                        300
aagtettttg gggteecaag teaaaaagat gagggattta eeagttetet aacettggta
                                                                        360
gccccagact ccaaactttg ccttctagtc ccaagaggct atcaaaaagc aaaggccatc
                                                                        420
ttccaccttc ttttccanaa cagcacacat tccagacagt acttgaaagc aggaacctcc
                                                                        480
ttatecetta aaaacetett ggaaneatet teeetetett gettetaeta tgettggeee
                                                                        540
acctancatt cncntttttc tggaaaccgg aaaaancttn tgacttnngt tggctacatt
                                                                        600
cagettggcc ceetacaatn tggtttecat etgecetaan gaaattttaa agggcaettt
                                                                        660
ttttntggcc cctgactttc nntttttagg gctttccccc angctttgcc cctttggtta
                                                                        720
aaggggttat tttccttccc cttttggaag
                                                                        750
<210> 660
<211> 849
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(849)
<223> n = A, T, C or G
<400> 660
teggateeac tagteeagtg tggtggaatt egeggeeege gtegaeggge agtagtggta
                                                                        60
tgcntntcta aatgttataa ttatttcaga attactctgc cagaaagtta tgatcataca
                                                                        120
tagaagagtt tgtagctaac tttgaaagta gtggaaagtg gttttcatgt attgtttggg
                                                                       180
ttaatttaat tttgattata tttggttttt agttcaggta atttttttgt tgaaaacttc
                                                                       240
aaatgacaat ttcttcatgg ttactaaaga tcactcatgt ggagtagttt cagatttttt
                                                                       300
tctgaataca tgtattactt ttagagatgt aaagatgtga aattactaag agagaaaccc
                                                                       360
atgtgatttg tttagtggat caaaagtcgg tagctccttt gatcctaagt gccactgata
                                                                       420
gttaaataga tactgaagct atgggcaggc tggattgata agaaaaaagg agacagagaa
                                                                       480
atgggaaatt gggaaagaac tgtgcaaata ggaaaaggag agagcaacag aacagaatta
                                                                       540
gtaccacagt gccgaagtgc cacctcaggt acttccatct cccatctcct gaagaattca
                                                                       600
gtaacagttt gcaaatggtc aacacaatca tttagtgatc ctggttgata ttttcaatac
                                                                       660
tttctgggga tttcttggct ggnttcaaaa gatgatgctg atagttttat tgcccctgaa
                                                                       720
ggtattctga agnttancat aatttattgg tcagtaaaat atttgaataa aagngganga
                                                                       780
```

<211> 650

```
aggaaaatct ggcntcttat tttgggatnt cngcnggggg aangaggata taattnaccc
                                                                       840
cggccttgg
                                                                        849
<210> 661
<211> 653
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(653)
<223> n = A,T,C or G
<400> 661
aacttaaget tggtacegag eteggateee tagteeagtg tggtggaatt egeggeegeg
                                                                        60
tegaceteca ttegtttett gteetttttt tteatttttt eteatgttet atteaettta
                                                                        120
ggtttctaag ataaatatta taaaataatt tttacttata aattattcac tgataccctg
                                                                       180
tctttaacat gtgaaatgaa ttcaaaagga atcttaatga gaaataatat actcatgatg
                                                                       240
tttaatagat ttgatttcga aataataagc cctctgaagt cctaagttaa aaataaagca
                                                                       300
acttqtttqa taatttttca tcaaqaatqt atctqaqtct ctqaqtaatt attaqtaqqa
                                                                       360
atattccatt atcacaatta cacagtataa gctatttagt ctaactttac caaaaaaggg
                                                                       420
agetaettea acaetgtgtg agaettttaa tgggtttgea ttgggtatge actattagea
                                                                       480
agataaccta ttttacagca gtgtttntta acctttccca tttatttgaa aggcagctaa
                                                                       540
gatatagtag ttaatntaan gggctgatgc atttatatta catgtagana atgggagata
                                                                       600
cnaaagggag ngggggana tnttttgnat tcnnaagctt cnttgncaat taa
                                                                       653
<210> 662
<211> 646
<212> DNA
<213> Homo sapien
<220>
<221> misc_feature
<222> (1)...(646)
<223> n = A, T, C \text{ or } G
<400> 662
aaacttaagc ttggtacccg agctcggatc cctagtccag tgtggtggaa ttcgcggccg
                                                                        60
cgtcgaccca gggacaggca gccagngctg gggtcaccag ggtcccctct tgggccctcc
                                                                       120
aanagcaaca gtactggcaa cagctgggat ttgctgagca cagactctgc agcaggctcg
                                                                       180
gttgagetet etgtgeetgt teetteatae cateeteaeg eccateeatg agatgggtee
                                                                       240
agctgttttc agatgagaaa atggcacagg aagctggtaa gtgacagtca gaaatgaatg
                                                                       300
ctggcagctt antccttgga cccaccgcag tgcaggacct tgctcaacag ggatcaccct
                                                                       360
tgtccgccac ctgttcatga ggccacccag ggtttgtgtg gtcatttgtc tcctttcatc
                                                                       420
tgcttgcctt caaccagetg ggtcattagg gctggggaac ccagacccca cacagtcctt
                                                                       480
ctcccagang ccagacacan nctncgccac agnaaggact tcagtccccg aancaaatgt
                                                                       540
ncctgggcgt anaaactgna gggnccccaa tccctggtgg ggtactgctt tgcactggng
                                                                       600
gaattcaccc ctcattgnna acctttccct nttnncaccc ctaaac
                                                                       646
<210> 663
```

<220>

```
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1) ... (650)
\langle 223 \rangle n = A,T,C or G
<400> 663
aacttaagct tggtacccga gctcggatcc ctagtccagt gtggtggaat tcgcggccgc
                                                                         60
gtcgacgtcg acgcggcgng ccgtttcgac gcagttgata catattatta tatactacat
                                                                        120
nggttttcta gaattaaaaa attaatgtgt agtgccagcc ctagatgtaa gttacatata
                                                                        180
tcaactctat ccaattttgt cagccataaa acttaccttt ttcacatact tctaactcta
                                                                        240
                                                                        300
acaatqtqaq aaatqtaqat cattqcaatt atacccacaa qqcaqatqqc tacatqcaga
atggatagca gaatctagct acttacgcta gccacatggt agacgttttt tcctttgttt
                                                                        360
ttgcaaaatt gcaatataag ttgcatatcg ttagagtgaa aagatgtaaa gaacccatag
                                                                        420
aagccagtga tgaaggacat ttatattttc acctttacaa angaccttaa aattgcctat
                                                                        480
gtggagcaga aactggagga gggcnaancc atcngtaaaa aaaattttgn tnctatttgg
                                                                        540
atttgggcac cattattacc tccccaggtn cctttttgnt ttaacctttc ttttaaaaaa
                                                                        600
                                                                        650
aataattcnt aatttttggg caaaaaaaaa caaggttttt atttaaattt
<210> 664
<211> 678
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(678)
<223> n = A, T, C or G
<400> 664
                                                                         60
taaaaatcta qactacacta ggaaattatt ttantatcag aagaatatca ggggtgtagt
actcatcana qctaaatgag agcgctttaa aaatgttagt ttgtcttccg ccatttctac
                                                                        120
agaaagctgc aatttcaggt tttcaaccta ataggtgata tttaagaaaa aaaaaaagca
                                                                        180
atequaaata qeeccaetge ttttacaaat catttttet ettetaggta tageetgtea
                                                                        240
ggtggcctaa tgtaattttt gacatctcta ggaattttaa tagaaccaga aatgggtgcc
                                                                        300
                                                                        360
agagatatgc ctgcactaat cttaagtggg gatttatgta tttctcaagc aagtgattaa
agcaaaacta ggcacgattg aaatcaanat cttttaggca agaaagtcat gatgagtttt
                                                                        420
anaattattt taggactctg tggctttctc ttcatagaaa tagaaaaaaa aaattgtata
                                                                        480
aaaaccacaa aaggtcctga atagcccaaa gcaacactga acaaaangaa caaagcagga
                                                                        540
aqcaacacac taccqqaatt caattatact accaaqqtqt antaaccaaa acaqcattct
                                                                        600
                                                                        660
attgggcata aaatagacca aagaccagtg ggaaacagaa taaagaancc caaaataaat
cctatattta cnqcccnc
                                                                        678
<210> 665
<211> 694
<212> DNA
<213> Homo sapien
```

```
<221> misc feature
<222> (1)...(694)
<223> n = A, T, C or G
<400> 665
cttttcaaat catttttnct cttctaggta tancctgtca ggtggcctaa tgtaattttt
                                                                      60
qacatctcta ngaattttaa taqaaccaga aatgggtgcc agaqatatgc ctgcactaat
                                                                     120
cttaagtggg gatttatgta tttctcaagc aagtgattaa agcaaaacta ggcacgattg
                                                                     180
aaatcaaqat cttttaggca anaaagtcat gatgagtttt agaattattt taggactctg
                                                                     240
tqqctttctc ttcatagaaa tagaaaaaaa aattgtataa aaccacaaaa gqtcctgaat
                                                                     300
agccaaagca acactganca aaaagaacan agcagggaag caacacacta ccngaattca
                                                                     360
aattatacta ccagggtgta gtaaccaaaa cagcattcta ttggcataaa atagacacca
                                                                     420
agaccaatgg ancagaataa agaaccccac aaataaatcc atatatntac cgccanctga
                                                                     480
ttatcaataa cnaacaccaa gaacatatnt taagggacnt nctattcaat aantagtgct
                                                                     540
ggnaaaaact gggaaatcca tatgcagaaa naatgaaact agacccctat ccctcaccat
                                                                     600
acqcaaannt caacttcqqa atqqqattac aaaacttaaq acattccaac ccaaqaaact
                                                                     660
atnaaancta ctattaagaa aacagatcnc nccc
                                                                     694
<210> 666
<211> 705
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(705)
<223> n = A, T, C or G
<400> 666
tttaaaaatt tagatacact angaaaatta ttttagtatc agaagaatat cagggggtgt
                                                                      60
agtactcatc agagctaaat gagagcgctt taaaaatgtt agtttgtctt ccgccatttc
                                                                     120
180
gcaatcgcaa atagccccac tgcttttaca aatcattttt tctcttctag gtatagcctg
                                                                     240
tcaggtggcc taatgtaatt tttgacatct ctaggaattt taatagaacc agaaatgggt
                                                                     300
gccagagata tgcctgcact aatcttaagt ggggatttat gtatttctca agcaagtgat
                                                                     360
taaagcaaaa ctaggcacga ttgaaatcaa gatcttttag gcaagaaagt catgatgagt
                                                                     420
tttanaatta ttttaggact ctgtggcttt ctcttcatag aaatagaaaa aaaaattgta
                                                                     480
taaaaccaca aaaggtcctq aatagcccaa gcaacactga acaaaaagaa caaagcagga
                                                                     540
agcaacaca taccagaatt caaattatac taccaaggtg tagtaaccaa aacagcattc
                                                                     600
tattgggcnt aaaatagacc naagaccaat ggaacagaat aaagaaccca aaataaatcc
                                                                     660
atatttttac agccagctna ttatcaataa aaacnccaag aacnt
                                                                     705
<210> 667
<211> 817
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(817)
<223> n = A, T, C \text{ or } G
```

```
<400> 667
nnangacttt tqtqqtntta tacaattntt ttttctattt ctatgaagag aaagccacag
                                                                        60
agtectaaaa taattetaaa aeteateatg aetttettge etaaaagate ttgattteaa
                                                                       120
                                                                       180
tcqtqcctaq ttttqcttta atcacttgct tgagaaatac ataaatcccc acttaagatt
agtgcaggca tatctctggc acccatttct ggttctatta aaattcctag agatgtcaaa
                                                                       240
                                                                       300
aattacatta qqccacctga cagqctatac ctagaagaga aaaaatgatt tgtaaaagca
qtqqqqctat ttqcqattqc ttttttttt tcttaaatat cacctattag gttgaaaacc
                                                                       360
tgaaattgca gctttctgta gaaatggcgg aagacaaact aacattttta aagcgctctc
                                                                       420
atttagetet gatgagtaet acacceetga tattettetg atactaaaat aatttteeta
                                                                       480
gtgtagtcta aactttttta aaaagacatg taatccgcgg agtttgtaac tcaaaacgag
                                                                       540
                                                                       600
tgcatctagg aggtatcgca agccgtttct ggattaaatt cccagctagc ttgcttgctt
agcaggggcg ggnaaanaag acatctgcag cctagggaag aaaacctttc gcattgttct
                                                                       660
                                                                       720
tacqtqttta cqttatttta tttcctanaa caaggcngaa ttgggactcg aatggttcag
ttggggtggg ggatcccctg gtncataaaa ngtcanaaag anggtacagg cggaacncca
                                                                       780
                                                                       817
agggtcgtcc tgcatttana ctcggaattt tggtgcc
<210> 668
<211> 826
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1) ... (826)
<223> n = A,T,C or G
<400> 668
cggggggnnt tacgtctctc tggacgcttt tattgtacca gggcgatccc agcccaactg
                                                                        60
taccattcga gtccctactc ctgccttgct ctagggaaat aaaataacgt aaacacgtaa
                                                                       120
gaacaatgcg aaagcgtttt cttccctagg ctgcagattg tcttcttcac cgcccctgct
                                                                       180
                                                                       240
tagctagcta gctagctggg aatttaatcc agaaacggct tgcgatacct cctagatgca
ctcqttttga gttacaaact ccgcggatta catgtctttt taaaaaagtt tagactacac
                                                                       300
taqqqaaaat tattttaqta tcaqaaqaat atcaqqqqqt gtaqtactca tcaqaqctna
                                                                       360
atgagagcgc tttaaaaatg ttagtttgtc ttccgccatt tctacagaaa gctgcaattt
                                                                       420
                                                                       480
caggttttca ncctaatagg tgatatntaa gaaaaaaaaa acaatcgcan atagcccact
gcttttacaa atcatttttc tcttctaggt atagcctgtc aggtggccta atgtattttt
                                                                       540
                                                                       600
qacateteta qqaattttaa taqaecaqaa atgggtgeca gagatatgee tgcaetaate
ttaaqtqqqq atttatqtat ttctcaanca aqtqattaaa gcaaaactag gcacgaatga
                                                                       660
aatcaaqatc tttaqqccaq aaatcatqaa nanttttana attattttan gaatctgtgg
                                                                       720
cttctcttct taaaatngaa aaaaaaattg tttaaaccca naaggtctga atacccaagc
                                                                       780
nccctgaacn anagaacaan gccggagcac cccctcccaa atcccc
                                                                       826
<210> 669
<211> 547
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1) ... (547)
```

<213> Homo sapien

```
\langle 223 \rangle n = A,T,C or G
<400> 669
cattqtqttq qqqaaaaaat qatttqtata aqcaqtqqqq ctatttqcqa ttgctttttt
                                                                         60
                                                                        120
tttttcttaa atatcaccta ttaggttgaa aacctgaaat tgcagctttc tgtagaaatg
gcggaagaca aactaacatt tttaaagcgc tctcatttag ctctgatgag tactacaccc
                                                                        180
ctnatattct tctgatacta aaataatttt cctagtgtag tctaaacttt tttaaaaaaga
                                                                        240
                                                                        300
catgtaatcc gcggagttag taactcaaaa cgagtgcatc tnggaagtat cgcagccgtt
nctqqatnaa attcccaqct tgctngcttg ctnagccggg gggcggtnaa aaaaacatct
                                                                        360
gcaqcccngg ggnaaaaacc ttcgcattgt tcttacgtgt ttacgttatt ttatttccct
                                                                        420
                                                                        480
nnaqcaaqqc nqqqanttqq ggactcgaaa tggtacagtt gggctgggga tcgcccttgt
tacataaaag ncgtccagaa gagggacggt tacaggcngg ganctccaaa ggtcagtccc
                                                                        540
                                                                        547
tgccatt
<210> 670
<211> 232
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(232)
<223> n = A, T, C or G
<400> 670
                                                                         60
cgaactattt agactaccta ggaaaattat tttagtatca gaagaatatc aggggtgtag
tactcatcag agctaaatga gagcgcttta aaaatgttag tttgtcttcc gccatttcta
                                                                        120
cagaaagctg caatttcagg ttttcaacct aataggtgat atttaanaaa aaaaaaaagc
                                                                        180
aatcgcaaat agccccactg cttttacaaa tcatttttc cccaacacaa tg
                                                                        232
<210> 671
<211> 214
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1) ... (214)
<223> n = A, T, C or G
<400> 671
                                                                         60
ctccccttcc ntccttcgct actncncatt ttcnnaaatt tntttcgcnt atgnggaaaa
                                                                        120
acacccacat tnttcanctc gcacagaaca ngnnggggtg tgtaaaatga agggcttccn
cnetttetet tattnaanaa caetnaaana qqqanqqqet aaaacceqeq ngatntetae
                                                                        180
                                                                        214
nctatcgcgg gcgcttttgg ngttggctag aaga
<210> 672
<211> 328
<212> DNA
```

```
<220>
<221> misc feature
<222> (1) ... (328)
<223> n = A,T,C \text{ or } G
<400> 672
                                                                          60
ngancagegg ngtttaaaeg ggeetetaga etegaggaga eneetgttgg atggtggate
acanntcgnt actactatac aggacagagt atcggganct cttggntgtt ggngcctgcc
                                                                         120
aaccactgct nctgttaact gcgtatctga agggactcgg actggcttca gaagaactac
                                                                         180
cqqctcqaat gnaccatgga tgattcncnc tagttgaaaa aaaactcagg cacatgtatt
                                                                         240
                                                                         300
qccactqatq actaqcqcca gactnctctc ggctctntaa cgagcccaca tgncngtgtg
                                                                         328
nenecegtge tgnetecaga agaggtte
<210> 673
<211> 223
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(223)
<223> n = A, T, C \text{ or } G
<400> 673
                                                                          60
qqqqqcaaaq ctggctagcg tttaaactta agcttggtac cgagctcgga tcccnnagac
                                                                         120
attqtqcatq aaaatgcaaa ttgagtgtgg tctatantgc catcntcacc tnctgncngc
                                                                         180
tcaaaacaac ngctttctgc tgcaatgggt agggctcctn acncacggtc gcnnacggag
                                                                         223
geennettat cetenteggt nnggateeet ngaageatnt tet
<210> 674
<211> 256
<212> DNA
<213> Homo sapien
<220>
<221> misc_feature
<222> (1)...(256)
<223> n = A, T, C or G
<400> 674
gnggggtent ngatgagege gegtaataen ateaethten ggegngntgg gtacegggee
                                                                          60
cccctcnaa gcggccgccc tttttttttt tttttcatn acatgataan ntctttnttc
                                                                         120
                                                                         180
taaacaqacc acaccactan aqttcctttn ctttngtacg gaattgagtt aaagtagagn
atacaatqca qqqcttcnnc tctatttcac attccaggnt ggttcngnat ggatcggccc
                                                                         240
                                                                         256
tqcctctccq atgggt
<210> 675
<211> 439
<212> DNA
<213> Homo sapien
```

```
<220>
<221> misc_feature
<222> (1) ... (439)
<223> n = A, T, C \text{ or } G
<400> 675
nnactagtec agtgtggtgg aattecattg tgttgggett gtatgggttt ttttgtetag
                                                                          60
ttntttggga aatgttngtg ttactatntt ttggatatna tatatgatat gtatggccct
                                                                         120
tctatgggct cctcanacng aactcaacca ttttccacaa aaccnattcc tcctttccct
                                                                         180
                                                                         240
tcatgactga gtggtgttgg tactatccng gaaactggga cattgtcctt cacatctntc
ccttanctgc ctngtccnat tgatgtcttt gagctntgan atgtctttgt taactntctc
                                                                         300
ctncntctgt actgccggca naattaagca ccatntgtca caaaaagtat tgcgttacct
                                                                         360
tcacgnatct gttngttncc atnettgetg etteteengn ggaaaatagg etnttetgge
                                                                         420
                                                                         439
aaccgaacng aanaaatac
<210> 676
<211> 587
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1) ... (587)
<223> n = A, T, C \text{ or } G
<400> 676
nggnggcctn attaagegeg egtaatacna etcaetntgg ggegaattgg gtaeegggne
                                                                          60
cccctcaaqt tnatntgccn aacctctctt ttggaataac aaaaggttta acacatatgt
                                                                         120
cctcataggg acgcgctttc acacnttcct gacngcttca tanacntcat tnctatttct
                                                                         180
                                                                         240
cctcagnaca agttnaggcn gaaggtgagg canacnttat aatttccatt tcacaaatnc
                                                                         300
ggaaagtgag getcaaaggg nttaaaaaaat aacetgatae aanteataga geeggtntet
ggaanaagca ggagcaaagt ccaggcatcc tgatccaagc tnggtccact gccttccact
                                                                         360
                                                                         420
ctggagaggc ttcatctccg acaaaggaag ggacntgagt ggctgganaa tctcatggga
taaagacctc agnatttcat gctcctggaa atcccatggg ttgaacaaca ggtntttggc
                                                                         480
ccgtggttct ntccctttgn ccatctttta accttggggt aaatgatggc ntctntnagc
                                                                         540
ntttttttn aaagagatng aaattgaatg attattngct cattggg
                                                                         587
<210> 677
<211> 444
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(444)
<223> n = A, T, C \text{ or } G
<400> 677
gtggggcatn attaagcgcg cgtaatacga ctcactatag gggcgaantg ggtaccgggc
                                                                          60
ccccctcgaa gcggccgccc tttttttttt tttttactgt ccaaactntc tatngatnta
                                                                         120
gttgaactgt ncaacgattt catgaaattc tatacacana gccttcaggt ccagagagta
                                                                         180
```

```
aaacaaattt aaatttnttc accanattgn agcagncana agcatccnat natatccgac
                                                                       240
tacaatgaat natatgctna nggtanctna tttacccact ntggggtctt tanggtctgt
                                                                       300
cacaaactat tttcgtaaac atcnntttaa anttnggtga atggacctaa tnccagataa
                                                                       360
ntctatttna tntaccctaq catnectqtq qctnactttn cgggctgtgt tggcntactt
                                                                       420
                                                                        444
ttaggagaaa attggtataa atnn
<210> 678
<211> 670
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(670)
<223> n = A,T,C or G
<400> 678
actagtccag tgtggtggaa ttccattgtg ttgggagcag tttaaaaaaaa aaaaagacna
                                                                         60
aatatacnac tottgatnaa acataaaggt acagtggtot atgaggaana gaaaaggtac
                                                                        120
                                                                        180
ctnaqqatqc aaaantacct accacatggg aaccgttngt ccacactcat tccnnanaaa
accqaqtcct ctcanttnca cacqtqtacq tttcaqttgg gaagtgcttg ccattactcc
                                                                        240
naagcctaga accttcacgt cctgaaggtt ctggaaggtt tttcagattg cttaaganac
                                                                        300
gengecette catattente tecaetacee nggggaaegg aacaaatgga getgegaeng
                                                                        360
ggaagcgtcc cttcccntcc gaacgctttc tttcaaacct gcctgccttc cnggcgaatg
                                                                        420
gaccggaagg tttnctngct tcctttcanc ccnaattact tcctgngttg aaaattggcc
                                                                        480
tgttggtttg caaatgengg aatttgttta etttenteat gteetgtgtt gnnenaaceg
                                                                        540
getenettgt tgcctccctt tngaaaggtt ttcatcagge cccgcccttt ctcttntaan
                                                                        600
ngtcctaatc cggncnggac cactcgggga aaattttttc ttttcgaaaa gccgccccnt
                                                                        660
ccgtccggct
                                                                        670
<210> 679
<211> 449
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(449)
<223> n = A, T, C \text{ or } G
<400> 679
actagtccag tgtggtggaa ttccattgtg ttgggagtag gtctactaca ncctacttcc
                                                                         60
                                                                        120
cctatcatan aagancttan caacnttcat gatcccccc tcntanncct tttcctcanc
tgcntcctag tcctgtttgt cctnttccta acantcntaa ganagatnac taatnctact
                                                                        180
atctctnacc tccggaanct acaanacgtc tggaactatt cngaccccat gcanccncat
                                                                        240
netceategt ceteceagee cetnecette etttaentta etnaacgaag gtegacgate
                                                                        300
cctcccntac ctcccnnncc attgggnccc aanggnactg gacctcacga ntacaccnac
                                                                        360
tacggggnga ctaagnctgn aactccttac atatntcccc gttacccccn gaacncagcg
                                                                        420
                                                                        449
aacngcnaca ccttggacnt caagaanta
```

```
<211> 670
 <212> DNA
 <213> Homo sapien
 <220>
 <221> misc feature
 <222> (1)...(670)
 <223> n = A, T, C or G
<400> 680
tttcngtgtg gtggaattcg cggccgcgtc gacgagaaga nggaggagga naaggagaag
                                                                         60
gagaagaagg agaanaagga ggagaaggag aagaaggaga agaaatcatc atcatcatca
                                                                        120
tccactgtct ngcaactatt taagtttgcn antcccttga aaacaggtac ttttgtttca
                                                                        180
atgtttggga ccactnctga cnatgannag aanaccaata aatgcttgat naatgaaaaa
                                                                        240
nccacttttt acctgttaga accctgaggc taagagaant gatgtgactc gacttagtta
                                                                        300
ccacaaacta tgatcctagc atnaattggg gcatctcaac acctcaactc cctgtgcaag
                                                                        360
aacagatttt caatgtctac tgatgatttt aaatggatta nttcctctct ttacttctta
                                                                        420
agggcatgaa gntttatgaa acaaaactat ncagttccag acgcttaacc cacatagtgt
                                                                        480
taatagtcac cttcaacaca cnactaaacc cccaaaaaan gntttttacg gngtttcgac
                                                                        540
agttttcttt tctttttgac ttgnttaaca cccnngacaa ctttgtnctn tttccntgaa
                                                                        600
tcacancttt cnaanancca atggtneggt tttttctcnt tengggeeet teeettnttn
                                                                        660
aaaaccanat
                                                                        670
<210> 681
<211> 494
<212> DNA
<213> Homo sapien
<220>
<221> misc_feature
<222> (1)...(494)
<223> n = A, T, C or G
<400> 681
tcatggtgtc cacagtctga tgtgagcgca ttaaatttaa ggatctccgc ccttctcctt
                                                                        60
aaaactcagg acttggcaat gancctagga agcgccctc ccctccccan ccanatccaa
                                                                        120
gccccggacc gctgcgnctc cagctgcgcc tagtgaaacc gccgaattcg aattcacact
                                                                        180
cggngggccg gcgaaggtgt gcgcgccgc gggagcgccg gggcnagccc gagggactgc
                                                                        240
aagccaanaa nggaggcatg ggtggcgggg ggcgccgtct gatccaggaa ggagcggagg
                                                                        300
cgccgatcac acactettna gacgccctgc ccgcgcctgg ccagcgcgca gnctgcagga
                                                                       360
cgcgcggagc aggaactcgc tggagtttgc caagccccan gnctctggaa agtntgtagc
                                                                       420
tecetttegg anegnetett etggeeettt gggaegggtg tgteattggg egggggtetg
                                                                       480
tataaggggg ggac
                                                                       494
<210> 682
<211> 263
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
```

```
<222> (1)...(263)
<223> n = A, T, C or G
<400> 682
tgatcattca agcgntgngc gnataacgat tgctnagccc aacctttcat agggtcgttc
                                                                         60
ctttgggaat nggatgtcta ttgaatggca gggatagggg cactcggcat tcgcctctgg
                                                                        120
tacagttttg catatatatc ctcatcgcga gcgagcgtag gggancgtta agtttgggga
                                                                        180
aatgccnccg catgnccctn ccggagctta aacccccaac aatncccatt ttnaaaaaag
                                                                        240
ntttnttant taaaaaaaaa aac
                                                                        263
<210> 683
<211> 255
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1) ... (255)
<223> n = A, T, C \text{ or } G
<400> 683
cttgcccggc atgcacagac ntntttacgg acacnetact ccaagngage ctgnanctqt
                                                                         60
ctacggtcaa nctctaaggt tngncantgc cacanatggc atagtcccga gggcggtnan
                                                                        120
tetggantge tetetgeaet tgaacntaaa gegentttea aganaggnet aatngeetge
                                                                        180
ctcttgacaa cnaacaancc cacaccnacc tangaccctn tangcaagga ctggattctg
                                                                        240
naaatgcaat acaca
                                                                        255
<210> 684
<211> 922
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(922)
<223> n = A, T, C \text{ or } G
<400> 684
accetteatt teatgtgett etatttteet acatetttta catqaetaaq qqattaatqa
                                                                         60
aatcacctct tcataatcat gaccataatt tcatccaaca agtactcaag tttggtgtta
                                                                        120
gcactttatt aatgettacg aattetetet etetecetet ttetetttte ettagteett
                                                                        180
gcacaataag gatttttgaa tgtataatat catcttaggt aagctttcat atggttttgg
                                                                        240
catatgaagc ttatgactgt cataagccat accaagcctg tggagtatgg catgattttc
                                                                        300
attacataat ccaatgaaaa tagacttatt ttaaatccct aactttgtag ttttaatttg
                                                                        360
tatttcacta tcttgaaatt aacagctagt acttatccat cacagcagtc tcctactgac
                                                                        420
atgaagcaag ttgttgaatg cagtaganca tgaatgaaag catttaatgt tanacaaaaa
                                                                        480
tgggtgatac ccaagcattc tgaattattt gcatcaagga atgggacatg tacattagtg
                                                                        540
gcatcatttc taccaatatg tgacttgaat tgttttttta aaaaaaggan aatgantttc
                                                                        600
tcaatttgct ttaaaaaatt ttnaaaaagt tcaatggcat gctgctttgt ctggacttaa
                                                                        660
tttattaaca attnttaanc cttccttaag gacanaattt tggtgttcag gatcnccctg
                                                                        720
aagggtctta tttttnatan nattccaaac ccaaaaggtg gtttaaaatg ggngggttcc
                                                                        780
```

```
ccccncnaaa atttggaccg gcttttttat atttaaaaaa nttnccnttt gngtttgaaa
                                                                         840
nctnaatacc aattaagggg gaattttacc tnccagtggg aaaaaaaaac nctngccntt
                                                                         900
                                                                         922
naaaaaattc ccnggagnca at
<210> 685
<211> 531
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1) ... (531)
\langle 223 \rangle n = A,T,C or G
<400> 685
tqaqqctctq taaaactqtt cctctqctaq qcatacttca tattctctat attaaactca
                                                                          60
tetttaattg geatggaaga tteattgtte caaateteag atgaagatee tatattggat
                                                                         120
qcaattaaqc ctqqcaqcqc cctcaaaaqa cagtcttqtc actgctagcc acagccagga
                                                                         180
cacagtaaca gttccttcta gtgacccnag accataanaa atananatct aaagaattct
                                                                         240
qactccaaaq qcattaqccc attcctqqta ttqccaatta tqataqaaaa aattqccaaq
                                                                         300
ctcctgggac atggaaatac actcagtaca tttgagaact ggagaactan tttccaaaat
                                                                         360
agtatgaaga catganggtg attgtagata tntgagtttg gagaanttga gggaaatcng
                                                                         420
attacacatg tttactacaa gagatgttna taagtaaaga aggcctgata tacaatctaa
                                                                         480
cagachantg agataaatct taantcacaa ctgachtccc ttttggggcg g
                                                                         531
<210> 686
<211> 336
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1) ... (336)
<223> n = A, T, C \text{ or } G
<400> 686
                                                                          60
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tcaaqaacac tacaaqctat gtcctcttct canaqagccc tgaantttta acatattgaa
                                                                         120
agetetnate ttgccaaana actecaetta actteaaaae acaeceteca cacaeateat
                                                                         180
gatcaactna gatcttactg aaccagaatc ctnaatggca tacttcagga acaggggtcc
                                                                         240
anagaagcag ttctcaaant gcagctnaaa aagaaactga aaacccaatt catgcaanac
                                                                         300
ctagggctta tttgagagca ttttccagtg cagatt
                                                                         336
<210> 687
<211> 271
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(271)
```

```
\langle 223 \rangle n = A,T,C or G
<400> 687
                                                                         60
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tttettttta agetgeactt tgagaactge ttetetggae eeetgtteet gaagtatgee
                                                                        120
atttaggatt ctggttcagt aagatctcag ttaatcatga tgtgtgtgga gggtgtgttt
                                                                        180
tgaagttnag tggagttctt tggcaagatc agagctttca atatgttnaa acttcaqqqc
                                                                        240
                                                                        271
tetetgagaa gaggacatag ettgtagtgt t
<210> 688
<211> 740
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(740)
<223> n = A, T, C or G
<400> 688
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                                                                         60
cqaaqcqqcc qccctttttt tntttttttg tqagaqttta aataaaatat ttgagtttaa
                                                                        120
tttaaagttt gagtttaatt aaaatatatg gcatatccca agttgggctt tgcanaaaga
                                                                        180
acacttetea ggaactgtta gttggtgtac caggaactea gaagggteet gttattaaat
                                                                        240
atatttggaa aatgcatgga ttctctgaan atcnctctgc atgtgagcaa cacttacatc
                                                                        300
ncaaaccaaa attqqcattq catacatnaa ccaatatttc ccaaacattt ctqqttatqq
                                                                        360
cccacccct ttgtgtanta cttattgctg ttttttggaa ccctggggaa attacttaaa
                                                                        420
atattcagct qqaaattaca qqcqttactt ttaaqqqanc aaqaattaca qtqactccca
                                                                        480
aaattgcaag tgttgattac tatttaagaa cccaagaatt tgaaagaaat tttgaaaagt
                                                                        540
gaaaacngga aatnttaaat gacttctcaa attttgaaaa ctcnggnaaa catctccact
                                                                        600
ttggtnccct tcctttaaaa attggctaaa aattntttnt tatncccacc ccattggaan
                                                                        660
tnccccccc ctqqaacaat tqqattcccc tatttcctaa aaaacqqccn cccccccqq
                                                                        720
ggngaacncc nacnttttgn
                                                                        740
<210> 689
<211> 635
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1) ... (635)
\langle 223 \rangle n = A,T,C or G
<400> 689
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                                                                         60
aaagaagtgt acaaagttga gatgtttcct gagctctcat atatctgana atgtcatttt
                                                                        120
acateteegt etteacetet caaaacttet tteaattett tggetettaa tagtaateaa
                                                                        180
cacttgcact ctggagtcac tgtaattctt gctcctttac agctacncct gttatttcca
                                                                        240
gctgaatatt tttagttatt tcccagggtt ccaaaaaaaca gcaataagta ctacacaaag
                                                                        300
```

ggggtgggcc ataaccagaa atgtttggga aatactggct catgtatgca atgccaaatc

tccaaatata ctgaaaaatg tcaaacttta	tttaataaca ttctttctgc	gggaaccttc aaaacccaac caattatttt	tganttcctg ttggggatat attttaaact	ttcaaanaat gntacaccaa gccatatatt cctcaaaaaa	ctaacagttc ttaattaaac	420 480 540 600 635
<211> 3923 <212> DNA <213> Homo	sapien					
<400> 690						
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gaattacaac	acatatactt	agtgtttcaa	tgaacaccaa	gataaataag	tgaagagcta	180
gtccgctgtg	agtctcctca	gtgacacagg	gctggatcac	catcgacggc	actttctgag	240
tactcagtgc	agcaaagaaa	gactacagac	atctcaatgg	caggggtgag	aaataagaaa	300
ggctgctgac	tttaccatct	gaggccacac	atctgctgaa	atggagataa	ttaacatcac	360
tagaaacagc	aagatgacaa	tataatgtct	aagtagtgac	atgtttttgc	acatttccag	420
cccctttaaa	tatccacaca	cacaggaagc	acaaaaggaa	gcacagagat	ccctgggaga	480
				ctgtgcctgg		540
				aggatgggca		600
				aaatgaagtc		660
				gcttcacaag		720
				ggggaggaga		780
				gttcataacc		840
				tctctacggt		900
				atttagttcc		960
				gttcaaagac		1020
				tctggcccag		1080
				cttactagca		1140
				gtctttgccc		1200
				gtcattccat		.1260
				catgcagcta		1320
				tttatccctc		1380
_				actgaggctg		1440
_		•		caacccctcc		1500 1560
				atacattatt agttttgaat		1620
	_			atcacatgag		1680
			-	tgaaatgcaa	-	1740
	_		_	agcaaaggca		1800
				acaatatcca		1860
_				atccatttca		1920
-				actttgagat		1980
-				ctttagggtt		2040
				agagetetgt		2100
_				cttgacccat		2160
			_	atgatgtatc	_	2220
_	-			taacataaaa		2280
	_			aaatctaact		2340
	J JJ	33	3			

```
gctacacact gcttgacata tattgttaga agcacctcgc atttgtgggt tctcttaagc
                                                                      2400
                                                                      2460
aaaatacttg cattaggtct cagctggggc tgtgcatcag gcggtttgag aaatattcaa
ttctcagcag aagccagaat ttgaattccc tcatctttta ggaatcattt accaggtttg
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gagaggatte agacagetea ggtgetttea etaatgtete tgaacttetg teeetetttg
                                                                      2580
tgttcatgga tagtccaata aataatgtta tctttgaact gatgctcata ggagagaata
                                                                      2640
taagaactct gagtgatatc aacattaggg attcaaagaa atattagatt taagctcaca
                                                                      2700
                                                                      2760
ctggtcaaaa ggaaccaaga tacaaagaac tctgagctgt catcgtcccc atctctgtga
gccacaacca acagcaggac ccaacgcatg tctgagatcc ttaaatcaag gaaaccagtg
                                                                      2820
teatgagttg aatteteeta ttatggatge tagettetgg ceatetetgg eteteetett
                                                                      2880
gacacatatt agcttctagc ctttgcttcc acgactttta tcttttctcc aacacatcgc
                                                                      2940
ttaccaatcc tctctctgct ctgttgcttt ggacttcccc acaagaattt caacgactct
                                                                      3000
caagtetttt ettecateee caccactaae etgaatgeet agaccettat ttttattaat
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ttccaataga tgctgcctat gggctatatt gctttagatg aacattagat atttaaagct
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                                                                      3180
tatattactg attgcactga acagcatggt ccccaatgta gccatgcaaa tgagaaaccc
                                                                      3240
agtggctcct tgtggtacat gcatgcaaga ctgctgaagc cagaaggatg actgattacg
                                                                      3300
                                                                      3360
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tgctccctgc cttcagtgtc ctctgcatct cccctttcta atgaagatcc atagaatttg
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ctacatttga gaattccaat taggaactca catgttttat ctgccctatc aattttttaa
                                                                      3480
acttgctgaa aattaagttt tttcaaaatc tgtccttgta aattactttt tcttacagtg
                                                                      3540
tettggcata etatateaac tttgattett tgttacaact tttettacte ttttateace
                                                                      3600
aaagtggctt ttattctctt tattattatt attttctttt actactatat tacgttgtta
                                                                      3660
ttattttgtt ctctatagta tcaatttatt tgatttagtt tcaatttatt tttattgctg
                                                                      3720
acttttaaaa taagtgattc ggggggtggg agaacagggg agggagagca ttaggacaaa
                                                                      3780
tacctaatgc atgtgggact taaaacctag atgatgggtt gataggtgca gcaaaccact
                                                                      3840
atggcacacg tatacctgtg taacaaacct acacattctg cacatgtatc ccagaacgta
                                                                      3900
aagtaaaatt taaaaaaaag tga
                                                                      3923
<210> 691
<211> 882
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(882)
\langle 223 \rangle n = A,T,C or G
<400> 691
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                                                                        60
cctgcactcc agcctggatg acagaacacg atcatttctc taaagacaaa caaaaaacat
                                                                       120
aaaataaaac tagtataagg atagaagccc agggttgatt taagtctgcg gaaatcataa
                                                                       180
accataggtc agacttctca ttgatgaggt acttgtgggt tagaatacaa ttaggtatat
                                                                       240
ttggtctaga aaccaggatg gaattagaga ataaaagact gagcaatagc atgttatagt
                                                                       300
attagaaata ctatagaaat aggaaaagcc ctgattatga ctttggagtt ctgatccaac
                                                                       360
atctgggatt atttagatat tttaaaggaa aacgatgact tttagctctc aggatgttag
                                                                       420
tttcctcaac cataaaatga agagcctcga aaagatttcg tttaccagat tatttctgaa
                                                                       480
gtcaattcca gttctaaaat tccatcactg ngcactaagg caaattgaat tgaataaagt
                                                                       540
attgggnatg cataaaatac tctattttta aaaangaata gtaattatcc attggnaaca
                                                                       600
gacgcantca tccagncatc tcctaccctg ncccatgncn tatgtagana tgtanctcta
                                                                       660
```

atcccttaac aaaccgattt tgcaaaggag cttanccttg gggtacttgg tcanggcaac

```
tggtctactt tnaagactca tcttcactta ctgggcacca aatncctacc attgcatcaa
                                                                       780
actggggttc ccatncaagg caaacctgn gaaatcttta atcccgaaat tggcgcccaa
                                                                       840
ttttgngggg tttccnaaaa gaatcntccc ccccgagggg cc
                                                                       882
<210> 692
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<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(235)
<223> n = A, T, C or G
<400> 692
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                                                                       120
cttctcanag cacttaatat gttaatataa aactncgnga aaaaagatnt tcnatgaanc
                                                                       180
nttcctctta ggaggtcagg ngagaatagt gttaatgnca ttaagganag aacga
                                                                       235
<210> 693
<211> 383
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(383)
<223> n = A, T, C or G
<400> 693
nttatgtaag aaatgtcata tatcttttat tttctttaaa tcaaaataaa tatgactttg
                                                                        60
aqcatcccat cccatgcccc atcctatcag aatggtagga acatcaacac aaataattag
                                                                       120
taatgcaccg catctacatt cccatgctct ctttacttct tcagcattgc ctaaaggcat
                                                                       180
aatacacctt taattaatta attcagcctc ctaatgcaca ttaacaaagc ccctgctaga
                                                                       240
ctctgtccat aatggnaaac ctgnatgatc cttgatatta acantttaag gaatgctcat
                                                                       300
                                                                       360
ggattggttn cagacttaaa aaattgaggg ggctgaanaa aatctaangg anaaatcatg
                                                                       383
gaagcatttg cacatattac ata
<210> 694
<211> 204
<212> DNA
<213> Homo sapien
<400> 694
tetettgget ggteageetg aagggtggta atgaeteace aaegetaeta ateettette
                                                                         60
actgtccctt atttttttcc ctcccaggct cataactcga ggttaaactc tcttttatac
                                                                       120
aagaaccctg tctgatgaag catcatttca gaattttaag tcaacttaca aatgtggtat
                                                                       180
                                                                       204
tattcacatc tgagtacaaa ttta
```

```
<211> 670
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(670)
\langle 223 \rangle n = A,T,C or G
<400> 695
gcaccageee aggtgetgtt tetteaettg ageteeatga eecteeetgt gtggtgggtt
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gaacggtgac ctccaaaaga tatgtccacc tggaacctca gaataagatc ttatttggaa
                                                                         120
tagtetttgt agatgteagt aaggtaaaga tttggagatg agaceeteet ggattagggt
                                                                         180
aggeectagg tecaetggea ggtgtgette teagggtetg aaaggggaag acagggeeae
                                                                         240
ccagaggagg agacggaggc agagacaggg ccacccagag gaggagacgg aggcagagac
                                                                         300
agggccaccc agaggaggag acggaggcag agacaggggc cacccanagg aggagacgga
                                                                         360
ggcagagaca gggccaccca gaggaggaga cggaggcaga gacagggcca cccaaaggag
                                                                         420
gagacggagg cagaanacag gccccccaa agaaganacc ggaggcanaa aacagggcca
                                                                         480
cccanaggag gagacggagg canaaacagg gccaccccaa aggaggagac ggaggcaaaa
                                                                         540
caqqqccacc caaaaqqaqq aaqccqqaaq qaaaaaacaq qqccccccca aaqqaqqaaq
                                                                         600
ncggagggcn aaaaanaggg cccccccaa agngagaaaa ccnggnaggc nanaaaaccn
                                                                         660
ggggccnnc
                                                                         670
<210> 696
<211> 317
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(317)
<223> n = A, T, C or G
<400> 696
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                                                                         60
gttagcaggg aagagaacag aattttatcc accettatct etttagtgag tgaacaaaca
                                                                         120
gcccactgtc atcgtggata catttcactt ttttcacatg actaaggagc tctccggagt
                                                                         180
gaagagtgag taaatatgtt tattacgcat tcatttgcta agaatcatca agaacccaaa
                                                                         240
gttagagacg tttcgtggtt gaactttctc cctactgtct agtagaatta tatggggatt
                                                                         300
ctggatctgc tggtgcc
                                                                         317
<210> 697
<211> 246
<212> DNA
<213> Homo sapien
<220>
<221> misc feature
<222> (1)...(246)
<223> n = A, T, C \text{ or } G
```

ggateetenn ttttttteet	aatcgactnc anagcggacg tnacagagnt gntacnnatg	cctactacta ntttttgtgc	ctaaattcgc ccttggttct	ggncgcgttg tatgctcana	acttttttg ctcngcaaaa	60 120 180 240 246
<210> 698 <211> 3674 <212> DNA <213> Homo	sapien					
<400> 698						
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	gtttagatta					120
	acatattcct					180
cacatcaatg	tcttagaact	tcttcacagc	ctgtttgatc	tggtgcttgt	tggctttaac	240
atccacaatg	aacacaagtg	tgttgttgtc	ttctatcttc	ttcgtggtga	ctcagtggtc	300
agcggaaact	tgatgatagc	gtagtggtca	agcttgtatc	tcctgggagc	gctcttccaa	360
agatatttgg	gctgcctcgg	gagttgcagc	gtcttgggcc	gccggaaggt	gggtgacgta	. 420
	ttttttgtgt					480
atccttcgct	ttggtttcgg	ctataggagg	ggcaggagct	tccttcttca	ctttcggcgc	540
catcttgtga	aaagggaaag	tttcctttct	aataccattt	tcacttctcc	cgaattttgt	600
ggatcgtttc	ttggtatcta	ccccagattt	caggagtgtt	ggctggatct	tagggattgt	660
gaagtcttca	tttccctgtg	gtgagatctg	aggcatgatt	ttaaacagtg	tgagggaagg	720
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	ggagaactag					. 840
	ctgcacagtg					900
	gtaaagcact					960
	tgaattcatc					1020
	ttgagaaaca					1080
	atgcacatcc					1140
	gtttcccagc					1200
	gacaggccct					1260
	aatgtgatat					1320
	aagcctgagg					1380
	gttgttacct					1440
	tgaacttagc					1500
	gatcaattgc					1560
	caatctattg					1620
	gctctctaat	-	-			1680
	tctagaaata					1740
	catcctttaa		_			1800
	gattggggga					1860
	acacatttgc					1920
	caacattgga					1980
	gcaacataga					2040
	actctttaag tgggaggctg					2100
	agtgacacct					2160
	aaaagtttaa					2220 2280
agacaaaaag	addayccaa	cyuuuyaaca	caycacaaaa	caaaccccct	yyacctaaaa	440U

```
gtatttttgt tcaagccaaa tattgtgaat cacctctctg tgttgaggat acagaatatc
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2400
aaatgagact aactaatcaa toogaggcaa ggggcaaatt agacggaacc tgactotggt
                                                                     2460
                                                                     2520
ctattaagcg acaactttcc ctctgttgta tttttctttt attcaatgta aaaggataaa
aactctctaa aactaaaaac aatgtttgtc aggagttaca aaccatgacc aactaattat
                                                                     2580
ggggaatcat aaaatatgac tgtatgagat cttgatggtt tacaaagtgt acccactgtt
                                                                     2640
aatcacttta aacattaatg aacttaaaaa tgaatttacg gagattggaa tgtttctttc
                                                                     2700
ctgttgtatt agttggctca ggctgccata acaaaatacc acagactggg aggcttaagt
                                                                     2760
aacagaaatt cattteteac agttetgggg getggaagte caegateaag gtgeaggaaa
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ggcaggette attetgagge ceetetettg geteacatgt ggecaecete ecaetgegtg
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gcactgtggg gtggggggtt gtggctgctc tgctctgagt ggccaagata aagcaacaga
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ggggacctcc aagtcggcca ccctggaggc aagcccccam agagcccatg caaggtggca
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gcagcagaag aagggaattg tccctgtcct tggcacattc ctcaccgacc tggtgatgct
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                                                                     3300
cagetgetea ggtggetgea aateattaca geetteatee tggggaggaa etgggggeet
                                                                    3360
ggttctgggt cagagagcag cccagtgagg gtgagagcta cagcctgtcc tgccagctgg
                                                                    3420
atececagte eeggteaace agtaateaag getgageaga teaggettee eggagetggt
                                                                     3480
cttgggaagc cagccctggg gtgagttggc tcctgctgtg gtactgagac aatattgtca
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taaattcaat gegeeettgt atceettttt ettttttate tgtetacate tataateact
                                                                     3600
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aaaaaaaaa aaaa
                                                                     3674
<210> 699
<211> 2051
<212> DNA
<213> Homo sapien
<220>
<221> misc_feature
<222> (1)...(2051)
<223> n = A, T, C \text{ or } G
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                                                                      60
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                                                                     120
tggatcccaa gactcagcat ccaaggtccc ctccaggaat cctggcagct cagcatactt
                                                                     180
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ttatactgta agtgagcaat cagagtataa tgtttatggt gacaaaatta aaggctttct 6960
tatatgttta aaaaaa
                                                                  6976
```

Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu Thr Gly 50 55 60

Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr Leu Ala Ser Leu 65 70 75 80

Tyr His Arg Glu Lys Gln Val Leu Ile Gly Gln Trp Val Glu Ser Gly 85 90 95

Trp Glu Gly Trp Ser Gly Phe Leu Gly Gly Gln Leu Ala Gln Asn Leu 100 105 110

Val Ser Gly Lys Gln Leu Trp Arg Met Leu Leu 115 120

<210> 707

<211> 150

<212> PRT

<213> Homo sapiens

<400> 707

Met Val Gln Arg Leu Trp Val Ser Arg Leu Leu Arg His Arg Lys Ala
5 10 15

Gln Leu Leu Val Asn Leu Leu Thr Phe Gly Leu Glu Val Cys Leu 20 25 30

Ala Ala Gly Ile Thr Tyr Val Pro Pro Leu Leu Leu Glu Val Gly Val
35 40 45

Glu Glu Lys Phe Met Thr Met Val Leu Gly Glu Ser Leu His Pro Pro 50 55 60

Ser Phe Leu Phe Gln Ile His Ala Thr Trp His Val Gly Gln Glu Tyr 65 70 75 80

Leu Cys Pro Gly Ser Cys Leu Glu Gly Glu Val Val Cys Trp Glu Gly 85 90 95

Ile Ala Gly Gln Glu Gly Asp Pro Gly Leu Arg Gly His Thr Lys Arg
100 105 110

Lys Lys Arg Ile Pro Arg Thr Tyr Pro Ser His Leu Trp Ile Pro Gly
115 120 125

Pro Ala Gln Ser Leu Ala His Arg Arg His Trp Arg Asn Ala Pro Asn 130 135 140

Leu Trp Leu Ala Leu Leu

<210> 708

<211> 371

<212> PRT

<213> Homo sapiens

<400> 708

Met Leu Phe Pro Ser Phe Ser Arg Ser Leu Val Pro Leu Pro Leu Ala 5 10 15

Leu Tyr Leu Ser Gln Pro Leu Thr His Thr Thr Ser Leu Leu Ala Gly 20 25 30

Ile Gly Pro Val Leu Gly Leu Val Cys Val Pro Leu Leu Gly Ser Ala
35 40 45

Ser Asp His Trp Arg Gly Arg Tyr Gly Arg Arg Arg Pro Phe Ile Trp 50 55 60

Ala Leu Ser Leu Gly Ile Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala 65 70 75 80

Gly Trp Leu Ala Gly Leu Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu 85 90 95

Ala Leu Leu Ile Leu Gly Val Gly Leu Leu Asp Phe Cys Gly Gln Val

Cys Phe Thr Pro Leu Glu Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro 115 - 120 125

Asp His Cys Arg Gln Ala Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu 130 135 140

Ala Leu Ala Pro Tyr Leu Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu 165 170 175

Leu Thr Leu Ile Phe Leu Thr Cys Val Ala Ala Thr Leu Leu Val Ala 180 185 190

Glu Glu Ala Ala Leu Gly Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala 195 200 205

Pro Ser Leu Ser Pro His Cys Cys Pro Cys Arg Ala Arg Leu Ala Phe 210 215 220 Arg Asn Leu Gly Ala Leu Leu Pro Arg Leu His Gln Leu Cys Cys Arg 225 230 235 240

Met Pro Arg Thr Leu Arg Arg Leu Phe Val Ala Glu Leu Cys Ser Trp 245 250 255

Met Ala Leu Met Thr Phe Thr Leu Phe Tyr Thr Asp Phe Val Gly Glu 260 270

Gly Leu Tyr Gln Gly Val Pro Arg Ala Glu Pro Gly Thr Glu Ala Arg 275 280 285

Arg His Tyr Asp Glu Gly Lys Ala Leu Ala Ala Ser Arg Gly Trp Cys 290 295 300

Gly Ser Arg Pro Pro Glu Thr Thr Leu Gly Ala Val Ser Gly Leu Val 305 310 315 320

Pro Leu His Pro Gly Pro Asp Phe Ser Val Arg Lys Val Gly Met Asp 325 330 335

Pro Ile Cys Ile His Gly Phe Ser Trp Val Trp Asn Ile Ser Ala Cys 340 345 350

Gly Phe Arg Lys Ala Ser Gly Cys Ser Arg Ser Leu Ile Arg Val Val 355 360 365

Ala Pro Val 370

<210> 709

<211> 141

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1)...(141)

<223> n=A,T,C or G

<400> 709

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<210> 710

<211> 196

<212> DNA

<213> Homo sapiens

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<223> n=A, T, C or G
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gtccncatcc acccgtcact ctccccntaa ncnataaccc cttttngcga atagacccca 120
cettancaat nggttttten ttttttgtee etnggneegn gegatteaan aaattgaagg 180
cccanaaaaa ccccct
                                                                    196
<210> 711
<211> 177
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(177)
<223> n=A,T,C or G
<400> 711
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tantctcgga tgtgcagtca caagtctttt gctaatnett ataattnten ctaccettte 120
ttcnacaata ctgctatcct anttnttctn tcncctctct cccannttac taaccac
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<210> 712
<211> 185
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(185)
<223> n=A,T,C or G
<400> 712
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ctggttgtcc gtgtcgcacg ganggccacg tccctctgnc ntgagtanca catagcatcc 120
acgtttagtc gactntnccg ggcggccgct ctacccntnt atngattctt attaaaantc 180
ggatc
                                                                    185
<210> 713
<211> 172
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (1) ... (172)
<223> n=A,T,C or G
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ggangagcac tnggtatgtt cacgtatene ttentaaana taenneeete eg
<210> 714
<211> 112
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(714)
<223> n=A,T,C or G
<400> 714
nttgcgtgcc tggacgtnta ctctgcanga tctactactc atgngaattc taantacgga 60
ctcactatnc ggcancgcag gcgcagcagg gaangggtca cctcccagtc tc
<210> 715
<211> 326
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(326)
<223> n=A,T,C or G
<400> 715
tactctanag gatctncgng tcatntggat tctatntcga ctcactctag ggctcnagcn 60
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gttctncaac gttcctgact nggaancece ngengtteng atcenenggt acctagetee 180
anntcecceg tnetcettet ggngtnteat naangaggae enceetegat enceetteet 240
taatctgcnc acnctgaacg nccaatggac atngtgcgtt taatntanna ggcccgnttc 300
                                                                   326
gngtgccctt cccgtnannt cagctc
<210> 716
<211> 122
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(122)
<223> n=A,T,C or G
<400> 716
nntgcgtcgc ctgngcgtnt actctagatg atctgantag tcatatggat tctaatacga 60
ctcannatag ggetetageg nggatnenga ttegtentee ngatteantg aeneeggtan 120
```

```
122
ca
<210> 717
<211> 203
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
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<223> n=A,T,C or G
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entgeatgee tgeaggtega etetagagga tetactagte atatggateg ageggeegee 60
cgggcaggtg tnaatgataa anatgcatca tactanccta cagaanggag agataatgtt 120
ngntggacca ngttggtttt cttgcgtgtg tgtggcagta gtaagttatt agtttttana 180
atcantaccg ccctccgcac cac
                                                                    203
<210> 718
<211> 168
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (1) ... (168)
<223> n=A,T,C or G
<400> 718
ggcagganga tenettgage ecengaggte gaggetacag tgagecanga gtgcactaet 60
gtnnegecet eegeatneae gngtggteeg ateeeegggt aceganetng antteaetgg 120
anttetttt aanegintig antggtaena ceetegante eetggetg
                                                                   168
<210> 719
<211> 210
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(210)
<223> n=A,T,C or G
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cancetcenc ataacaceta ttttntgatn aagattetna etgacecatn aantetaent 60
ctcaagctct tncanngtcc agtnaangga atgtgtatnn gtngggatnc cacanaaaaa 120
aganathtcg gncgcttcat tantcatcct tcttacccan ntctctngat ncncagtntg 180
ancntgaacg cacactacng gatntctcca
                                                                   210
<210> 720
<211> 131
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<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(131)
<223> n=A,T,C or G
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tocatoctaa tacgactcac tatagggctg ccaacctgcc atccactact gaggaagacc 60
cgnanactta ggggctcact gcgagccacc ggccacaggt cgtatagggc aaagcacgng 120
gaagcacccc t
                                                                   131
<210> 721
<211> 121
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(121)
<223> n=A,T,C or G
<400> 721
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naggaaaaan ganccaacaa ctaaaaaaaa nncggncgtg ncagcttnga tgactngtcc 120
                                                                   121
<210> 722
<211> 246
<212> DNA
<213> Homo sapiens
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<221> misc_feature
<222> (1)...(246)
<223> n=A,T,C or G
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gnttentega tatgaanaac actaateeca tgtngtntgn gteteegtga tteateecte 120
gcacnggtcc ccntccnaac cnttgcatag gtgttatgtt gtantctccc cagtgcacaa 180
agattnacac teteteantg tetganatat geaegagtte attgteetgt encegtnaac 240
atcaag
                                                                   246
<210> 723
<211> 160
<212> DNA
<213> Homo sapiens
<220>
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<221> misc feature
<222> (1) ... (160)
<223> n=A,T,C or G
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acgtcctcct cccccagnt aggattnana aaaggnctcc cagancaaaa nctccaaagt 120
gnatchanta gccgtncccg anathcaacg cccctacgtc
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<210> 724
<211> 156
<212> DNA
<213> Homo sapiens
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<221> misc_feature
<222> (1)...(156)
<223> n=A,T,C or G
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gageetttee aetttetae taataaaaaa atgeaceage eectaeeann agtgnggaaa 120
acctccttag gcccttgnnt ggaacaancg aaaatc
                                                                    156
<210> 725
<211> 347
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (347)
<223> n=A, T, C or G
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gagecegegg neagaegece cateagtage gteegeaceg ggnageegeg gntetegece 180
gageegtggg egegeeegag gggeggete geeteeegee gteeetegea getetgeegg 240
gcccgagccc gcgccgtcgc cgccgccgnc ttgccgctcg gnccgcgcgg nccggnaaac 300
gcggtcgagg tctggatgng gcanngcccg cncctntcgc tgagcct
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<210> 726
<211> 162
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(162)
<223> n=A,T,C or G
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tcccgccttt tnggtnccca aaganacnaa gggggagtcc cttnatagag gnagngcgat 120
nenteneaac nacntngaet ttgnecatgg ggagnaaggt gg
<210> 727
<211> 120
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(120)
<223> n=A,T,C or G
<400> 727
gtgtgggtgg ggaattccat tgtggttggg ggnaaatctc cgcttgtcca aagnacaggg 60
ggggtenett anagngnagg gggtteetee ceaecacttg nettgneeat tgngagnaag 120
<210> 728
<211> 130
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (130)
<223> n=A,T,C or G
<400> 728
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aattccatgt gtcgagagag gggcaaatac nctccaanac ancnccctca tgctcnacac 120
atattcgcat
                                                                   130
<210> 729
<211> 182
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(182)
<223> n=A,T,C or G
<400> 729
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gctggctgct tccagtcgat tanatttgtg aaaaagctga accncngccn gttaaggggg 120
annatgcaaa anatncatcc nnctgccccn taaactgntc tntccnaggg aaaaaangga 180
                                                                   182
ag
```

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<210> 730
<211> 678
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
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<223> n=A,T,C or G
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ctcggggctg ggggaccttc cccagtgacc atctcacttt ggctgaancc cactcggggc 120
agectgagtt tggggetett ggeettetea eecteetegg eeceeteett ggeeegeace 180
aggccaaacc ggggcagccg taccttgagc ttgtgtccgg cctctccctc cccctctgcc 240
acctggtact cggcatggtt gccccggga tggcgagagc tccacgtcgg gcagtgagaa 300
gcagaaagta cgctcggccc ctgggggctg ctcctcagca ccctcgcccc ccaccctagc 360
tetggeece agtgtgggea aetteageet eageecacee tegeetgtgg eegeetegee 420
cgcctgtgcc tctcggctta gccccacgtc caactcaagc tggggcactg tcacggtggg 480
catcttaaag acaccctcac ccaccagcag ctcaccacct gcaacctggg ctccaggcaa 540
aaaaagggtc acctggggca nctgaaccct gtacctgctg tgccctctgc tgaanggaat 600
gttatctgaa cctgctgccc tgggggtact gccttcccaa aaccgggtca antccacctg 660
                                                                   678
ttggaaggna aatncccc
<210> 731
<211> 135
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (135)
<223> n=A,T,C or G
<400> 731
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atatetttgg aagagegete eeageecaae acaatggaat teeaceacae tggnntagtg 120
gatccgagct aagcc
                                                                   135
<210> 732
<211> 660
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(660)
<223> n=A,T,C or G
<400> 732
gettggtace gagetnggat ceetagtaac ggeegeeagt gtgetggaat teggetttet 60
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tcaatcagnt nacgagetge atggtetget aacattgtea taattgetgg catagattae 120
tgaaaataaa gaaaaaaaat tgaagctgcc tatcaagttt tggtattatc aaaaacttcc 180
tacaagttat tttacttcaa ccatgttatt acaaatattt taatgaatac tttagagact 240
ttaattacaa aaaactgaga tagtaaaagc aagtaataaa agctgaaatt acttagctat 300
ttgataatta cataaattat tatggtccat tcaacttttc tagtgtttag tttatacacc 360
aggaagactt tcctattcta ctaacattta taaagtatgc taacctatta tttaaacgca 420
tccactatta ggattttatg gcctaaaacg tgatacagtt cagtatcttg atgtcaaaac 480
tttttaagca agtagggatt aagttcaagt gaatgtgatt ttctttcttc ccagtagggt 540
cttctgaata actcagnaaa gctcacttcc attatcttac tttataaaaa aatgctataa 600
gacagaatgg gccgacgtgg nggctccacc tgtatccacc ttttggaggcg agnggcgaat 660
<210> 733
<211> 836
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (836)
<223> n=A, T, C or G
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tagctactca ttttctggtc cacgaaggtt cctaaaatgg gaagaagtgg agatctgacc 120
ttgttagttc taaatacact aaactgggag tgccatggat ggctttcagg atgtcctgaa 180
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catatattca gtaaatatgt ttgtagcttt atttcaatcc cccaattcat tgagggttga 660
aacaatttga atggtttgag tgtagaagct aagttatttc tgtagaggct aagggcattt 720
ataccaanat atgttagact tgnggntcct gttaaccatg ctgtanacaa taggaattac 780
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<210> 734
<211> 694
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(694)
<223> n=A,T,C or G
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nagtnetatt theactaaac tgngagtgee ttggatgget tteaggatgt cetgaateet 60
ctataattgt atacaaaatc gtgagttttt aaaaactggg ttagagctat tggttcctca 120
gagteteagg catettagae ecceaaaaag gttaaggaet aetgaettaa ecaattaggt 180
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```
ttgagtggca ttggctttga agaaaagcag aggaaagata tattttataa ttctgggcaa 240
caaaaaaqtq qatqtqcc aqcatcttag agtagaatcc tcttaaaaqq atagcactqc 300
atatgaacta gtaggtttta accagtgcat atttaggcga agtagctcat ttttctgtta 360
qaattetttt ttatttqqqa atqqqcaaqe ttttacaqet tttacettqc caatqaatac 420
ctqqaattta aaaaatcttg ttaggcatat tgcccataaa gttttttttc ctagatcata 480
tattcagtaa atatgtttgt agctttattt caatccccca attcattgag ggttgaaaca 540
atttgaatgg tttgagtgta gaagctaagt tatttctgta gaggctaagg gcatttatac 600
caagatatgt tagacttgtg gttcctgtta accattgctg tagacaatag gaattactgt 660
atatccacat tttaattttt aacatcattc tgtc
                                                                  694
<210> 735
<211> 126
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (126)
<223> n=A,T,C or G
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ncnttgaaac nggttgacca gacttcaggc ctgtgcgctc aatcgtggag aatctcgtgc 60
cquattcqqc acquattct ctctctctt ctctctctt ctctctctt rtctctct 120
                                                                  126
ctctct
<210> 736
<211> 165
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (165)
<223> n=A,T,C or G
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cagaagcett taaaceggtt ngaccagact tcaggcetgt gegetcaate gtggagaate 60
tegtgeegaa tteggeaega gtetetetet etetetetet etetetetet etetetetet 120
ctctctctct ctctctctct ctctctctct ctctctctct
                                                                  165
<210> 737
<211> 125
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (125)
<223> n=A,T,C or G
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<211> 739

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cqtqccqaat tcgqcacqaq tctctctctc tctctctct tctctctctc tctctctct 120
tctct
<210> 738
<211> 137
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (137)
<223> n=A,T,C or G
<400> 738
ggagnenett gancaggatg accgaettea ggeetgtgeg eteaategtg gagaateteg 60
tgccgaattc ggcacgagtc tctctctct tctctctct tctctctct tctctctct 120
tctctctc tctctct
<210> 739
<211> 970
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(970)
\langle 223 \rangle n=A,T,C or G
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cggaattcgc ggccgcgtcg acggcccttn gtgccactag ntctttcatt cttccccccc 120
atcaatcagt gaacttttta gcctactcaa agctttgctc caatgcatag gatttatgat 180
tgtggggatt tccagataat ataaatattc aacatgaata ttttaaatta aggcatgaga 240
catttttcct aactgagcat agccatgaac ctctcacgtc tgttcctctg tgtcagtttg 300
tancactgaa tacagcagcc ctcctaaaag tccaggcagt gcacaggtct tgacatgatg 360
aagtgacgtg ttgctatggt gattttgcag ctggccaaat agtcactggt tgattttacc 420
cagcaggaga tttttgcaaa aatttcctgg gtgagagtga aatcaaactc ctattttgnt 480
tctcctctgc aagctgnagt taagatggat taatgagtac ttttagatta attaactctg 540
aagagaaaat gggagaaaag tgaggaaggt tgttggcaga agtcattgct ggaatccttc 600
tgaagggagt actgacttca cttgcaaaga cnagagacta naagacaatg aagttaaact 660
tggcctgtct ctcatatgat agatgctgag agtcaggntc agggaaattt aattctgtca 720
tacgcatatn ggattatgtg gtcatggatt tgttggcact aaccngcctn taatcagnat 780
aagaaaagtg ttttggtaga naaagaaaat tatggcccag aaaaacctgg aanacttgga 840
aaaaatgntn gggggccttg ggtggtggtc tnaaaanacc ccctggggat ntttaaacca 900
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gctttgctcc aatgcatagg atttatgatt gtggggattt ccagataata taaatattca 180
acatgaatat tttaaattaa ggcatgagac atttttccta actgagcata gccatgaacc 240
tctcacgtct gttcctctgt gncagtttgt agcactgaat acagcagccc tcctaaaagt 300
ccaqqcaqtg cacaggtctt gacatgatga agtgacgtgt tgctatggtg attttgcagc 360
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tgagagtgaa atcaaactcc tattttgttt ctcctctgca agctgnagtt aanatggatt 480
aatgagtact tttagattaa ttaactctga agagaaaatg ggagaaaagn gaggaaggtt 540
gttggcagaa gtcattgctg gaatccttct gaagggagta ctgacttcac ttgcaaagac 600
aagagactan aagacaatga agttaaactt ggcctgtctn tcatatgata gatgcttgag 660
agtacaggnt cagggaaatt ttaattctgn catacgcata ttggattatg tgggtcatgg 720
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<211> 1171
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gggatttcca gataatataa atattcaaca tgaatatttt aaattaaggc atgagacatt 240
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ccanggggaa agaaccttta ggnaaaggaa acccatttgg gaangggttt naaaaccntt 780
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gtttggaaaa nnaaanaaaa aaaattnaan ggncccnaaa aaaaaccctg gaaaaccttt 1020
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<220>
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gctttgctcc aatgcatagg atttatgatt gtggggattt ccagataata taaatattca 180
acatgaatat tttaaattaa ggcatgagac atttttccta actgagcata gccatgaacc 240
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tgagagtgaa atcaaactcc tattttgttt ctcctctgca agctgnagtt aanatggatt 480
aatgagtact tttagattaa ttaactctga agagaaaatg ggagaaaagn gaggaaggtt 540
qttqqcaqaa qtcattgctg gaatccttct gaagggagta ctgacttcac ttgcaaagac 600
aagagactan aagacaatga agttaaactt ggcctgtctn tcatatgata gatgcttgag 660
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<210> 743
<211> 610
<212> DNA
<213> Homo sapiens
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<221> misc_feature
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<223> n=A,T,C or G
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gtcaaattgc cctatatatg gagtaataaa cacgatttaa agaaatgagg actaaaaaaa 180
gattatatat aacccaacat aaaggcaacc tettaggegt tgacagaaac tgacaacttt 240
ttatctgtgg gtgcgatcca ttataagtaa cctgagcacc ttattttttc tttttaaact 300
ctaggtagga tacccgaggt ccacaaattt ttcataagaa atattttttc tctgccctat 360
gagattttaa aaaatattat actgcttcaa ttgcatcaaa agaaatggac cctaatatct 420
atgatgaagg atttggagtt agaagacctg agtttcaatt ttggcatggc tgtttgtcta 480
gctctgngat cttggacagg tcaattgact tggcttaatc ttctcatcca tttagnggag 540
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610
  ataangcctt
  <210> 744
  <211> 127
  <212> DNA
  <213> Homo sapiens
  <220>
  <221> misc feature
  <222> (1)...(127)
  <223> n=A,T,C or G
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                                                                      127
  gagagag
  <210> 745
  <211> 458
  <212> DNA
  <213> Homo sapiens
  <220>
<221> misc_feature
  <222> (1)...(458)
  \langle 223 \rangle n=A,T,C or G
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  acttectggg cettegggte tetgtgeact ggggtggete etgtggeeca gaatgeeetg 180
  gagaagggtc ctactggaag cgaaggtgca gggcagcagg gcctgaggcg caggagctgg 240
  tggaggetee cageacaggt egeegeeeca gteacateae tgetgatggt ggggggaett 300
  ggggagtttc ccccgagaat gggaggtctc acagtccccg tgctgcaatg ctgtcggtgc 360
  actgngncng caatgtgctc atggncactt gctttttctc tgtggccccg gccgatttat 420
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  <210> 746
  <211> 893
  <212> DNA
  <213> Homo sapiens
  <220>
  <221> misc_feature
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  <223> n=A,T,C or G
  <400> 746
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  canngaaagt cctgccgact tcctggggaa gcccatccgc acgtggggtg agggtcccca 180
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gagagggggc tacttgctgg ataaancggc cggggccaca gagaaaaagc aaggtgacca 660
tgagcacctt gcaaacacag tgcacccacc agcatttnag caccngggac tgtgaagacc 720
teccatttet teggggggaa aenegeecaa ngtteeecee acenteaeta gtgnattgtg 780
acctgggggn cgggccgacc cetgtngctt gggnnagccc tccncccagg tttctnnggc 840
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<213> Homo sapiens
<220>
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atttcaaatt tgaggtgaga gttggataag taagaataaa gctgctcttc aaagagatga 180
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tanaaatttg gatacttact gatcctacat atgtaacagg gagagaaggt gaatttcaaa 480
gcantaaatt gaaaaattgt tcacaatttc attttttaaa aaaagggagc taacagaaga 540
agaggttaat gtggtaatta taggatgnct cttgcgacac atgaatgnat ctggtatcat 600
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ngtcccaaaa cctcaccacc ttggagaaat natttccttt tgggggtntc attaaancct 720
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<212> DNA
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<222> (1)...(647)
<223> n=A,T,C or G
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<211> 642
<212> DNA
<213> Homo sapiens
<220>
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<223> n=A,T,C or G
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tacttctagt aaatggggac ctagtgcttg acttcccgga atagggatct atgcgaagtc 480
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cataacgact cctccaggaa agataaagaa tctcacatat agaacgggac cccatacacg 600
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<211> 639
<212> DNA
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agaaggcgct agtactcgga acttcacttc atctcggtag tttactttgg cgtatatagc 180
cttctccctc gaagactagc cgtcacattc gttccctagg aatcgtttct gcccctaaga 240
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agcaaagctc atgatttccc acacegegag agegectata accetatece atttettegg 420
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gttatcgagg atattacgat caagccgaga gaaccgctag aaccgctttc ttcgctttct 480
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<223> n=A,T,C or G
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aanacggtgg atacctaaat cgagtgngtt cattaaaagt agttgattac nccctaaaat 180
aanaanaggg cttcgtcggg anaaatcggt aagganaagt ctttntggca tcataanaat 240
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gcttaaatgg cgatactgct atagcgggtg agcgttggtt ctcgagnaan aaagcgtgtc 540
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<222> (1)...(644)
<223> n=A,T,C or G
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cctagggtcg gngaatttac ggttcgaaaa acggtagtnc ctaanggnty ntattngggg 600
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<211> 721
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<223> n=A,T,C or G
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gettgtgagt entgtacaca actcaggagt gtgacacage taccagettt cetectaact 180
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qttttqtaqq cttttttcc ccttctttcc ctctctcagc ttctccctgc ttctcagaan 300
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<211> 721
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<211> 782

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<213> Homo sapiens
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<221> misc_feature
<222> (1)...(721)
<223> n=A,T,C or G
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qcttqtqaqt cntqtacaca actcaggagt gtgacacagc taccagcttt cctcctaact 180
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<211> 873
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<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(873)
<223> n=A,T,C or G
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gcttaatcag tctgaaagtt aaactgacag tgttaagtta cggaatcaat gacatttagg 360
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cacacccatt accatgtggg tgctttacag catactgacg gaaggactga ggagccaccg 540
gagcaggagt tecteteagg gaggaegetg acaetteeae agetgeetan gtatgggeae 600
ctgatgccaa cgaanaaccc aaagcgctct cccttccaga tggaagctgc cccacactgg 660
getgacagea tetggagetg etetggetea aateeeggaa tegeacanet eetanegggg 720
gcgtttanag atcctcnggg ccagctaccg accacttttg acaagggnct taggagcgat 780
aactagnctg gcgcgttaca cncggatgga acgtcttgga cttgagacct cttgggggan 840
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atggcncccc caaataantt gggaaaantn ggg
<210> 757
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```
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(782)
<223> n=A,T,C or G
<400> 757
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ggatttgaga ccaggagaca gctccagatg ctgtcagccc agtgctgggg gcaggcttcc 120
atctgtgaag tggagaggcg ctttgggctt cttcgttggc atcaggtgcc catacctagg 180
gcagctgtgg aagtgtcagc gtcctccctg agaggaactc ctgctccggt ggctcctcag 240
teetteegte agtatgetgt aaageaceca catggtaatg ggtgnggact ggtaccatga 300
ctgntccctt aaaaggtggc cttcccnaag aaaggagaat tcttggacna gggatttcac 360
ttgnttagaa atgggaaaaa ttacccatta gaattttcgn ttccaaggcn tnaagnccta 420
aaaggeettt gatteeegaa eettaaeeet gggeagttaa eettteaaac gggataaaee 480
ctgangggga aaatnaaatc ctttaaaaaa gggggggttt naaggagggc tctttggctt 540
tcaggcantt gccaacctgg gaaattcana ggggaagtnt ttttttttgc ctgcctaggg 600
aacctttact taaacnaacc cttgnccccc catttggggt tgactttcan cctaattgct 660
gaaaggaccg ggccgntttt gntttccttt gncccaaagg naaanaaacg ggtgccantt 720
cccangggat tanttcccga aaatttggnn aatttttntt tgnaactttt tgggtttttt 780
                                                                   782
CC
<210> 758
<211> 647
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(647)
<223> n=A, T, C or G
<400> 758
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gggaagagcg ccgtcggtcc gagtacagta tggagtagta tagtcttcgc gccttctcgg 120
geggegggge tattetete aaaggeagag gteeetagte gaeetegete eeetaggtta 180
ggaacagccg tcgaatattt taggttcgtc gaggctttct tccgagctct acgcctaagt 240
ageteegega geaaagtate ggteatttte eestateeat eacteeecta agtaegeete 300
attattccgg aaggcaagag gccagcattc ctccttagag tagagggtag gtacctccgt 360
cgcgtgccgc gaaagggcag agcttcgtgt cttccctccg cagcagctta acggtctacg 420
taggegttet egatetttte aegggaateg gggteeggga gggeggegga aaaegtegae 480
gteteggtea eegteaeege eeegaacaac tageggettt eegettteaa etgaggaace 540
ccgcacccct cattagcgct tacgaaatcg gggangtgat tgcgccaatt cgttagcctt 600
cgataattat tctctattag cggtcctatc tcgcgctttc gatttat
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<210> 759
<211> 657
<212> DNA
<213> Homo sapiens
```

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<220>
<221> misc feature
<222> (1)...(657)
<223> n=A, T, C or G
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tgtagtagta ggtactgcgg gaaggcgaag agtcctttca aggacgattt acttaagttg 180
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gataggttgg gacttaaggc gaataagaag gaggcggcgg aggtcgcgat taccgcagag 300
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attoctaaga togotocogt ogagtatact agogacgaac gtaagagtgo cotoacaaga 420
accggtacaa actcaagaag aagttcccat taagcatcgt aagaaacggt aggacgagga 480
cggtaagaag taatcggaga aaggatccta gtngttacga agaagcatcg ttnagctact 540
ttgcgctacc gtttatattt agacgtgttc cgtccttctc cgtgtttana aaaaaggttt 600
atteegaegg gagaettagg egaatggagg gtteegeggt tganaategg anegggg
<210> 760
<211> 644
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(644)
<223> n=A, T, C or G
<400> 760
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ggaaaagaag taagcctcga agcctatctc cgaccgtatt tatttcgcag aagacqgaac 120
tacggacgtc gttaaccccg agtagccccc gtaagaaagg actaaagcga atggaaaagt 180
cgggaattcc ggcggagggg cggcgattac tgaaaggagt aagagtaaga ctattgcgat 240
acttgaggcg ttccctctta aaaggcaccc gaaacactct attaaaaaac acccgaagaa 300
gaacaactca tgcgatcggc cgtgtgcagc cgtcaatagt aaagagagcc atgaaccatg 360
ccatccttag accaattagg atgaagaaga ggaggaagat gaggaccaaa ccctacccac 420
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cgcactctcg tagcgcggac cgaatagaaa accggaaact acagctaaag ggtcctttcc 540
ggcctgttat ctacccaccc gcaatccgat cctcccccc cctcgtccaa aaaccctaac 600
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<210> 761
<211> 647
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(647)
<223> n=A,T,C or G
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<400> 761
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ggcgggtact ctctgggata atcggtataa gtgttgtaaa attgggggta agagaaagtt 120
tcattataag aagtggaagc acgagccggg gtgtttagtc gttaatatta agaccggttt 180
ttgttgtact tatatagctt gegegtgggg aggeaataag aaacattgeg tttegaggee 240
ggatgcgggg aaccetette ggggtetaga gegeegeate tgeaaaataa ggaetaetga 300
cgccgctcat aacgtactca acaatgagtc ggcctgcatt aagatttcgg cgaagaaccg 360
tactgcgtct actgatagta tattgcattg atagcggcat gagctttatc acgtgtcgtt 420
ttcgggttgt aagaagggag ttaagtcgat cttcgaggaa gaagagaccc caaataaaaa 480
atgactcaaa aaaacctaga agaaacacga cgaaaggaaa aagaacgtta aaactagtag 540
ctcttcggan gagtagcctt agtagggtaa gtcctccgtg cgtactgtcc taaggtttgg 600
atagcgcggt tgaatagacg gtcacgcgtc agaaggtaaa aanccgg
<210> 762
<211> 628
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(628)
<223> n=A,T,C or G
<400> 762
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tgtgttccct ttattcgctt gtattaatat ttgcgtagtg gattaaacaa atacttggtg 120
ttgactgtca gtcttagagg actgactaga agtagttttc atttggggct caggaaatac 180
ctactttata tttctagcta attaggaaag tcatttttca gttaggttgg tgttttggtt 240
caqqcactcg ctagctagat gacctaacat gctacttaat ttctgagtgt ttgtgtccat 300
ccctgtagga ttgttgcggg gttaaatgaa attgtgtata tttgtaaagc atttacctca 360
gtgcccagac tgtgacagag tagattatta ggcttgctct tatttctgtg attaaattta 420
gtgtcagatt agcaacctat agctacttct aaagctgctg ctgctttctt tgtttagggt 480
taggaagaaa catgctggac agtttgccaa atgagagtta catgatgtgg cttgtgggaa 540
cattctaact tggaacttgc ccatttccag gactttgngg ttcanagatt tttggggata 600
gatgtaaggg ttaaaaaaaa cngaaaac
                                                                  628
<210> 763
<211> 147
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(147)
<223> n=A,T,C or G
<400> 763
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gaaaagctaa ctggataact tacagcatgt ttctgccaat aatctcttan aacaggcctc 120
                                                                  147
tttttttat gcacaccacc ttcnggc
```

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<210> 764
<211> 146
<212> DNA
<213> Homo sapiens
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<222> (1) ... (146)
<223> n=A,T,C or G
<400> 764
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agagttaggg ggactgttag aacagagaaa ganatcatgg ggttgggttt gagtctgatg 120
nnnaactggt gccgnntgct cagtat
                                                                    146
<210> 765
<211> 129
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(129)
<223> n=A,T,C or G
<400> 765
tncncgattc gntnctagcg tntacactna tgtcttggta ccgagctcgg atccactagt 60
ccagtgtggg nggaattcca ttgtgttggg gcaggaggng ctttgngtac ngtgcggctg 120
nagaggcgg
                                                                    129
<210> 766
<211> 175
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (175)
<223> n=A,T,C or G
<400> 766
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tctggggctt ggnttttctc ctttgtanaa tgatgccttt ctgtggtttt gtcatttcta 120
acattetgtg ngtgatgagg tgtatatteg anganeteta tenecanagt actet
<210> 767
<211> 602
<212> DNA
<213> Homo sapiens
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<220>
<221> misc_feature
<222> (1)...(602)
<223> n=A,T,C or G
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cctggtttgt tttcagtgtt taatcctatt agtatcagca ggatataggt caggatatca 120
ggtgcagaac ctgtggaatc agccaatttg gcttgctcat ttactttaat aaggtcccat 180
aatgagtgag agtacaaagt tcaagccctg ttgagggtct gcattaaact ctcagaagta 240
tttagagtgt gccaggagcc gcgaaggtct ggttcgggtg gtggcgggaa ctgtattaga 300
gtgctaggca cggcgcgaca aagtctgtcc aacccaaaac ggtgctgagg cgttgggtgt 360
gagetecagt acteagaaaa geateteage aggtaeteaa eagateetea ggggettggg 420
ggcccagcac tggcagtgag ggcatgaaag acataaaagg gcactacctg tgggtatttt 480
ctgttctcca aggaggaagt agcaaaaatt aggacgctgg aatatcctat qttqtaqcaa 540
tcccagaaca actgatgctc aacaaatacc acacaaaaca aattttttaa aatttaatct 600
                                                                   602
<210> 768
<211> 671
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(671)
<223> n=A,T,C or G
<400> 768
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tegeggeneg egtegacaaa aataetgeta aagtaatatt tttatagatg actatttgee 120
ttggggccag gaaaagcagc tggagttatt cacttagtac catttttaca tactaacttt 180
gccttttcca tgcttgcttg atgcggcttg cagcactgaa gaacagtttc aattgctagc 240
caaccagaga gcatgatcaa accaaacaag ttccctgttt caggaaaaac aggttttagg 300
taactgaagg gttaccagtt actgattcca caatcttctc tgtaaaanat ttctgcctat 360
tatgcagact gggcggcttt aaanntggta aaactatnaa atacccatac aatattttaa 420
nggggccccn ttatnaagct tttcaggcct tcccctttcc atagcattgg tgggatacaa 480
gaaaccttta aacagcaacn agctatcnag gcccaaaaqq aaaqtaattn tqatttttta 540
nagattccgn aacgaaaaaa tggctgggtt caaatacnac cttcttttta aaatqqnttc 600
cttattaaac ntttttttt tttaatttta ccccatggtc ntgatnttng ngcttccgcc 660
canaaaatng n
                                                                  671
<210> 769
<211> 877
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(877)
<223> n=A,T,C or G
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ggtttgttct tcacttggct aacccctctt ttacttaagc acaccttgaa cattccctcc 180
ttccccattt ccccgcagng cccctaatgg acatacttct gaataacaca ggtggtattc 240
cttccttgtt ggaacctcct ggaggaagag acagatgatt aacaaatcct tccatcaacc 300
cctttgacca tgacatcaac agtgctccaa attatggggt accgtattaq cctatqtcta 360
tettgateag aateettace teggtgtatt gaaattatet atttegtgee tgeetettta 420
aagtcagggt ttgccttatc tattgtctaa caccatgcag taggtaacat gcagtaggaa 480
acatggcatt aaattatttg ggttcaaatc ccagttatgg tgtgtaaatg cctaccaggc 540
cgtgaggcac ctgctaagca ggttgcacgc atcatttgaa ttcacaccac ccttttgcaa 600
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aggattccca ccaaggcctc anggcccagg tccanggacc atgtctgttg tgacaactgg 720
agtgcatttc atatcccctn ctctgngggg naaggtccct cncgnggaga acnnttaaaa 780
caatcatnic ingggggnit aatgetiett neeccagtgi ggineactge ngecacqaqt 840
cccanccact agtcccangt ctgtcatgaa ccanccc
                                                                   877
<210> 770
<211> 874
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(874)
<223> n=A,T,C or G
<400> 770
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gaattegegg cegegtegae etttteaaag gttaaettat ttaattatea cannngeaac 120
ccgatgagta ggtaacagta ttttactgat aqqtaatcta aaqaaqqaqq ctaaataaat 180
tgcccaattt cgaacagtga gaggaagaat taggattgaa acacatatag tggcttcaga 240
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cctctcgtgt gtcccttttt tttagctatt tcagaagcac actqqtqcaa tattttacqa 660
aatgagtttc ttccccttac ctctgcatcc tctaagaaaa aatcattgnt gttttatgaa 720
natgaanatc ctgctatttc atatcttgat tggagctgct taattaaatg accattttna 780
aatttgtttt gattccnngc aaaaaaagtt tnttnttgga tgtagggggc tcnnaaagnc 840
caaaaccccc caaaattttt nnttgggaac ccna
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<210> 771
<211> 156
<212> DNA
<213> Homo sapiens
<220>
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<221> misc_feature
<222> (1)...(156)
<223> n=A,T,C or G
<400> 771
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gtgtggtgga attcgcggcc gcgtcgaccg cgagcggtcg cccttttttt tttttttt 120
ngtttttttg aanaattcat tgggtattta ttattc
<210> 772
<211> 586
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(586)
<223> n=A,T,C or G
<400> 772
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tggtggaatt cgcggccgcg tcgatcacaa agtgctcaca agtccngnat ttattttatc 120
tccagatatg aaacttaccc ccagctatgg tcttctattt gttatttaat ttctaggcca 180
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gcttattgag caggtattgt aggctaaaca attctanact ttaaggggac acagnttgca 420
aaacaaaatc ctgccttgna tggatactta tgnnatggng ggatacagac aatcaacata 480
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<210> 773
<211> 2983
<212> DNA
<213> Homo sapiens
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catgggagtt ccaaacgagc agtcctgtgt tccggcgagg acaggtgttt cacctgcggc 180
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actacaactg gcaggcaacc cttcaaaatg agtctggcaa agaggtcaca gtggctgtca 360
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teettaagte tgaagaaaac ateetatace ttetetteaa eecatggtgt aaagaggaca 480
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aaaatgteet ggaetgetge attteeetge tgaetgagag eteeeteaag eecacagata 660
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ggacaggcag tgccccgatc ctgcagcagt actacaacac gaagcaggct gtgtgctttg 840
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cacgcagtgt gacaggette gatteagete acgacacaga aaggaacete acggtggaca 960
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Asn Gln Pro Leu Gln Ser Tyr His Gln Leu Lys Leu Glu Phe Ser Thr 50 55 60

Gly Pro Asn Pro Ser Ile Ala Lys His Thr Leu Val Val Leu Asp Pro 65 70 75 80

Arg Thr Pro Ser Asp His Tyr Asn Trp Gln Ala Thr Leu Gln Asn Glu 85 90 95

Ser Gly Lys Glu Val Thr Val Ala Val Thr Ser Ser Pro Asn Ala Ile 100 105 110

Leu Gly Lys Tyr Gln Leu Asn Val Lys Thr Gly Asn His Ile Leu Lys
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Ser Glu Glu Asn Ile Leu Tyr Leu Leu Phe Asn Pro Trp Cys Lys Glu 130 135 140

Asp Met Val Phe Met Pro Asp Glu Asp Glu Arg Lys Glu Tyr Ile Leu 145 150 155 160

Asn Asp Thr Gly Cys His Tyr Val Gly Ala Ala Arg Ser Ile Lys Cys 165 170 175

Lys Pro Trp Asn Phe Gly Gln Phe Glu Lys Asn Val Leu Asp Cys Cys 180 185 190

Ile Ser Leu Leu Thr Glu Ser Ser Leu Lys Pro Thr Asp Arg Asp 195 200 205

Pro Val Leu Val Cys Arg Ala Met Cys Ala Met Met Ser Phe Glu Lys 210 215 220

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- Asp Thr Tyr Val Asn Glu Asn Gly Lys Lys Ile Thr Ser Met Thr His 305 310 315 320
- Asp Ser Val Trp Asn Phe His Val Trp Thr Asp Ala Trp Met Lys Arg 325 330 335
- Pro Asp Leu Pro Lys Gly Tyr Asp Gly Trp Gln Ala Val Asp Ala Thr
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- Thr Ala Ile Arg Lys Gly Asp Ile Phe Ile Val Tyr Asp Thr Arg Phe 370 375 380
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- Asp Ile Thr Tyr Glu Tyr Lys Tyr Pro Glu Gly Ser Ser Glu Glu Arg
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- Lys Thr Ala Ala Leu Gln Asn Val Asn Ile Leu Gly Ser Phe Glu Leu 500 505 510
- Gln Leu Tyr Thr Gly Lys Lys Met Ala Lys Leu Cys Asp Leu Asn Lys 515 520 525
- Thr Ser Gln Ile Gln Gly Gln Val Ser Glu Val Thr Leu Thr Leu Asp 530 535 540

Ser Lys Thr Tyr Ile Asn Ser Leu Ala Ile Leu Asp Asp Glu Pro Val 545 550 560

Ile Arg Gly Phe Ile Ile Ala Glu Ile Val Glu Ser Lys Glu Ile Met 565 570 575

Ala Ser Glu Val Phe Thr Ser Phe Gln Tyr Pro Glu Phe Ser Ile Glu 580 585 590

Leu Pro Asn Thr Gly Arg Ile Gly Gln Leu Leu Val Cys Asn Cys Ile 595 600 605

Phe Lys Asn Thr Leu Ala Ile Pro Leu Thr Asp Val Lys Phe Ser Leu 610 615 620

Glu Ser Leu Gly Ile Ser Ser Leu Gln Thr Ser Asp His Gly Thr Val 625 630 635 640

Gln Pro Gly Glu Thr Ile Gln Ser Gln Ile Lys Cys Thr Pro Ile Lys 645 650 655

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Asn Gln Pro Leu Gln Ser Tyr His Gln Leu Lys Leu Glu Phe Ser Thr 50 55 60

Gly Pro Asn Pro Ser Ile Ala Lys His Thr Leu Val Val Leu Asp Pro 65 70 75 80

Arg Thr Pro Ser Asp His Tyr Asn Trp Gln Ala Thr Leu Gln Asn Glu
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- Ser Gly Lys Glu Val Thr Val Ala Val Thr Ser Ser Pro Asn Ala Ile 100 105 110
- Leu Gly Lys Tyr Gln Leu Asn Val Lys Thr Gly Asn His Ile Leu Lys
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- Ser Glu Glu Asn Ile Leu Tyr Leu Leu Phe Asn Pro Trp Cys Lys Glu 130 135 140
- Asn Asp Thr Gly Cys His Tyr Val Gly Ala Ala Arg Ser Ile Lys Cys 165 170 175
- Lys Pro Trp Asn Phe Gly Gln Phe Glu Lys Asn Val Leu Asp Cys Cys 180 185 190
- Ile Ser Leu Leu Thr Glu Ser Ser Leu Lys Pro Thr Asp Arg Asp
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- Pro Val Leu Val Cys Arg Ala Met Cys Ala Met Met Ser Phe Glu Lys 210 215 220
- Gly Gln Gly Val Leu Ile Gly Asn Trp Thr Gly Asp Tyr Glu Gly Gly 225 230 235 240
- Thr Ala Pro Tyr Lys Trp Thr Gly Ser Ala Pro Ile Leu Gln Gln Tyr
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- Tyr Asn Thr Lys Gln Ala Val Cys Phe Gly Gln Cys Trp Val Phe Ala 260 265 270
- Gly Ile Leu Thr Thr Val Leu Arg Ala Leu Gly Ile Pro Ala Arg Ser 275 280 285
- Val Thr Gly Phe Asp Ser Ala His Asp Thr Glu Arg Asn Leu Thr Val 290 295 300
- Asp Thr Tyr Val Asn Glu Asn Gly Glu Lys Ile Thr Ser Met Thr His 305 310 315 320
- Asp Ser Val Trp Asn Phe His Val Trp Thr Asp Ala Trp Met Lys Arg 325 330 335
- Pro Tyr Asp Gly Trp Gln Ala Val Asp Ala Thr Pro Gln Glu Arg Ser 340 345 350
- Gln Gly Val Phe Cys Cys Gly Pro Ser Pro Leu Thr Ala Ile Arg Lys 355 360 365

- Gly Asp Ile Phe Ile Val Tyr Asp Thr Arg Phe Val Phe Ser Glu Val
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- Asn Gly Asp Arg Leu Ile Trp Leu Val Lys Met Val Asn Gly Gln Glu 385 390 395 400
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- Ser Thr Lys Ala Val Gly Gln Asp Arg Arg Arg Asp Ile Thr Tyr Glu 420 425 430
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- Asn Ser Val Asn Phe Thr Val Ile Leu Lys Arg Lys Thr Ala Ala Leu 485 490 495
- Gln Asn Val Asn Ile Leu Gly Ser Phe Glu Leu Gln Leu Tyr Thr Gly 500 505 510
- Lys Lys Met Ala Lys Leu Cys Asp Leu Asn Lys Thr Ser Gln Ile Gln 515 520 525
- Gly Gln Val Ser Glu Val Thr Leu Thr Leu Asp Ser Lys Thr Tyr Ile 530 535 540
- Asn Ser Leu Ala Ile Leu Asp Asp Glu Pro Val Ile Arg Gly Phe Ile 545 550 555 560
- Ile Ala Glu Ile Val Glu Ser Lys Glu Ile Met Ala Ser Glu Val Phe 565 570 575
- Thr Ser Asn Gln Tyr Pro Glu Phe Ser Ile Glu Leu Pro Asn Thr Gly 580 585 590
- Arg Ile Gly Gln Leu Leu Val Cys Asn Cys Ile Phe Lys Asn Thr Leu 595 600 605
- Ala Ile Pro Leu Thr Asp Val Lys Phe Ser Leu Glu Ser Leu Gly Ile 610 615 620
- Ser Ser Leu Gln Thr Ser Asp His Gly Thr Val Gln Pro Gly Glu Thr 625 630 635 640

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<212> PRT

<213> Homo sapiens

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Thr Lys Asp Ser Lys Ala Thr Glu Asn Val Cys Lys Cys Gly Tyr Ala
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Gln Ser Gln His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp 65 70 75 80

Asn Tyr Lys Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp 85 90 95

Ile Gln Phe Glu Thr Leu Gly Lys Lys Gly Lys Tyr Ile Arg Leu Ser 100 105 110

Cys Asp Thr Asp Ala Glu Ile Leu Tyr Glu Leu Leu Thr Gln His Trp
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His Leu Lys Thr Pro Asn Leu Val Ile Ser Val Thr Gly Gly Ala Lys
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- Val Arg Leu Phe Leu Glu Asn Gly Leu Asn Leu Arg Lys Phe Leu Thr 465 470 475 480
- His Asp Val Leu Thr Glu Leu Phe Ser Asn His Phe Ser Thr Leu Val 485 490 495
- Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala Leu Leu 500 505 510
- Thr Phe Val Trp Lys Leu Val Ala Asn Phe Arg Arg Gly Phe Arg Lys 515 520 525
- Glu Asp Arg Asn Gly Arg Asp Glu Met Asp Ile Glu Leu His Asp Val 530 535 540
- Ser Pro Ile Thr Arg His Pro Leu Gln Ala Leu Phe Ile Trp Ala Ile 545 550 555 560
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- Ile Ala Gly Ile Val Phe Arg Leu His Ser Ser Asn Lys Ser Ser Leu 805 810 815
- Tyr Ser Gly Arg Val Ile Phe Cys Leu Asp Tyr Ile Ile Phe Thr Leu 820 825 830
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- His Asp Val Leu Thr Glu Leu Phe Ser Asn His Phe Ser Thr Leu Val 485 490 490
- Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala Leu Leu 500 505 510
- Thr Phe Val Trp Lys Leu Val Ala Asn Phe Arg Arg Gly Phe Arg Lys 515 520 525
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- Ala Asn Glu Tyr Glu Thr Arg Ala Val Glu Leu Phe Thr Glu Cys Tyr 610 615 620
- Ser Ser Asp Glu Asp Leu Ala Glu Gln Leu Leu Val Tyr Ser Cys Glu 625 630 635 640
- Ala Trp Gly Gly Ser Asn Cys Leu Glu Leu Ala Val Glu Ala Thr Asp 645 650 655
- Gln His Phe Ile Ala Gln Pro Gly Val Gln Asn Phe Leu Ser Lys Gln 660 665 670
- Trp Tyr Gly Glu Ile Ser Arg Asp Thr Lys Asn Trp Lys Ile Ile Leu 675 680 685
- Cys Leu Phe Ile Ile Pro Leu Val Gly Cys Gly Phe Val Ser Phe Arg 690 695 700
- Lys Lys Pro Val Asp Lys His Lys Lys Leu Leu Trp Tyr Tyr Val Ala 705 710 715 720
- Phe Phe Thr Ser Pro Phe Val Val Phe Ser Trp Asn Val Val Phe Tyr 725 730 735
- Ile Ala Phe Leu Leu Leu Phe Ala Tyr Val Leu Leu Met Asp Phe His 740 745 750
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- Tyr Ser Gly Arg Val Ile Phe Cys Leu Asp Tyr Ile Ile Phe Thr Leu 820 825 830
- Arg Leu Ile His Ile Phe Thr Val Ser Arg Asn Leu Gly Pro Lys Ile 835 840 845
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- Thr Thr Tyr Asp Phe Ala His Cys Thr Phe Thr Gly Asn Glu Ser Lys 915 920 925
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- Trp Ile Thr Ile Pro Leu Val Cys Ile Tyr Met Leu Ser Thr Asn Ile 945 950 955 960
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- Val Gln Glu Tyr Cys Ser Arg Leu Asn Ile Pro Phe Pro Phe Ile Val 995 1000 1005
- Phe Ala Tyr Phe Tyr Met Val Val Lys Lys Cys Phe Lys Cys Cys 1010 1015 1020
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- Lys Ile Asn Thr Lys Ala Asn Asp Thr Ser Glu Glu Met Arg His Arg 1060 1065 1070
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